(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 May 2004 (21.05.2004)

PCT

(10) International Publication Number
WO 2004/041799 A1

(51) International Patent Classification[7]: C07D 285/10, 417/10, A61K 31/433, 31/4427, A61P 3/10

(21) International Application Number:
PCT/GB2003/004721

(22) International Filing Date:
3 November 2003 (03.11.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0225986.9 7 November 2002 (07.11.2002) GB

(71) Applicant *(for AE, AG, AL, AM, AT, AU, AZ, BA, BB, BE, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CY, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, FR, GB, GD, GE, GH, GM, GR, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, SZ, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW only)*: **ASTRAZENECA AB** [SE/SE]; Sodertalje, S-151 85 (SE).

(71) Applicant *(for MG only)*: **ASTRAZENECA UK LIMITED** [GB/GB]; 15 Stanhope Gate, London, Greater London W1K 1LN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BIRCH, Alan, Martin** [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). **KENNY, Peter, Wedderburn** [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield, Cheshire Sk10 4TG (GB). **MORLEY, Andrew, David** [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). **RUSSELL, Daniel, John** [US/US]; AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, MA 02451 (US). **TOADER, Dorin** [US/US]; AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, MA 02451 (US).

(74) Agent: **ASTRAZENECA**; Global Intellectual Property, P O Box 272, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4GR (GB).

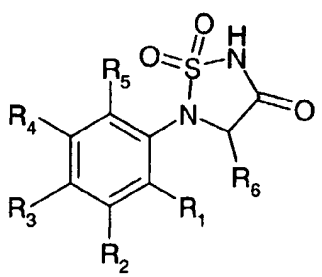
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

[Continued on next page]

(54) Title: 5- (SUBSTITUTED PHENYL) -THIADIAZOLIDINE-3-ONES AND THEIR USE AS PTP1B



(I)

(57) Abstract: The invention concerns compounds of the formula (I) or pharmaceutically acceptable salts thereof (A chemical formula should be inserted here - please see paper copy enclosed herewith) wherein R_1, R_2, R_3, R_4, R_5, and R_6 have any of the meanings defined in the description. Processes for the manufacture of compounds of formula (I), compositions containing them, their use as inhibitors of protein tyrosine phosphatase PTP1B and their use for the treatment of diabetes mellitus are also described.

WO 2004/041799 A1

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

5-(SUBSTITUTED PHENYL)-THIADIAZOLIDINE-3-ONES AND THEIR USE AS PTP1B INHIBITORS

This invention relates to chemical compounds, or pharmaceutically acceptable salts thereof, more particularly to certain substituted thiadiazolidines or pharmaceutically acceptable salts thereof, which inhibit protein tyrosine phosphatase PTP1B and are accordingly useful in methods of treatment of the human or animal body. The invention also relates to processes for the manufacture of said compounds, to pharmaceutical compositions containing them and to their use as therapeutic agents.

Protein phosphorylation is a post-translational event, which is responsible for the regulation of most cell signalling pathways. This phosphorylation is regulated by enzymes which either act to phosphorylate (protein kinases) or dephosphorylate (protein phosphatases) proteins. Protein phosphatases are divided into two major groups, i.e. those that dephosphorylate proteins which contain phosphorylated serine or threonine residues (Ser/Thr phosphatases) and those that dephosphorylate proteins which contain phosphorylated tyrosine residues (protein tyrosine phosphatases or PTPases). Unlike the protein kinase family, there is no sequence identity between these two groups of phosphatases. The PTPases are a large family of enzymes, which all contain the PTP signature motif in a highly conserved region of approximately 250 amino acids that make up the catalytic domain. The invariant cysteine residue has been shown to be critical to PTPase activity (reviewed by Cheng et al, Eur.J.Biochem. 269:1050-1059 (2002)).

The PTPases can be subdivided into three different classes, namely classical tyrosine specific PTPases; dual specific PTPases and low molecular weight PTPases. The classical tyrosine specific PTPases can be further subdivided into two groups: (i) receptor-type PTPases, which include CD45 and LAR, and which consist of an extracellular domain, a single transmembrane domain and most have two tandem repeated cytoplasmic PTP domains (although generally only one is active); and (ii) intracellular PTPases, which include PTP1B, TC-PTP and FAP, and which contain a single catalytic domain. The numerous amino and/or carboxyl domains may be involved in the subcellular localisation or regulatory function of these intracellular PTPases.

Initial analysis of the data generated from the human genome project has identified approximately 120 human protein phosphatases and a role for members of this family of proteins in disease is becoming clearer. Of the total, there are 42 PTPases, which have the potential to act as both positive and negative regulators of cell signalling. A number of these

PTPases have been shown to play a vital role in the regulation of cell signalling pathways associated with metabolism, growth, proliferation and differentiation, such that abnormal regulation may lead to a number of important disease states including diabetes and cancers (reviewed by Zhang, Annu. Rev. Pharmacol. Toxicol. 42:209-234 (2002)).

Insulin plays a key role in the control of blood glucose and defects in its synthesis or signalling lead to insulin resistance, diabetes and its associated complications. The glucose lowering and other effects of insulin are a consequence of insulin binding to its receptor and the subsequent activation of a number of downstream signalling cascades. Phosphorylation of tyrosine residues in a number of proteins in the insulin signalling cascade is critical to this signalling process. The insulin receptor is a tyrosine kinase that is autophosphorylated on tyrosine residues following activation by insulin. The phosphorylated insulin receptor catalyses the phosphorylation of its downstream substrates, including the insulin receptor substrates (IRSs). Removal of insulin itself is not sufficient to "switch off" these insulin sensitive signalling cascades. Dissociation of insulin is followed by dephosphorylation of the insulin receptor and of other components of the signalling cascade. A number of PTPases have been implicated to dephosphorylate proteins essential to this pathway, and as such are termed as negative regulators of insulin signalling (reviewed by Johnson et al, Nature Reviews Drug Discovery 1:696-709 (2002)).

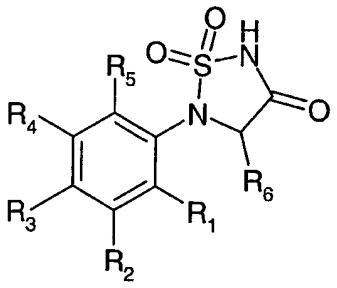
PTP1B was the first PTP to be purified to homogeneity. It was purified from human placenta, cloned and subsequently identified as a PTPase, shortly afterwards. Data generated in vitro, using a tri-phosphorylated peptide corresponding to the catalytic region of the insulin receptor kinase domain, showed that the activity of this peptide could be inhibited following dephosphorylation with PTP1B. Experiments involving cells in culture using antibodies, and antisense oligonucleotides suggested PTP1B to act as a negative regulator of insulin signalling (Ostman and Bohmer TRENDS in Cell Biology 11(6): 258-266 (2001)). Generation of PTP1B null mice further supported this hypothesis (Elchebly et al, Science 283:1544-1548 (1999)). PTP1B null mice are phenotypically normal with a normal lifespan, as compared to their wild type littermates. However, PTP1B null mice demonstrate tissue specific up-regulation of the insulin receptor (in liver and muscle) and improved insulin sensitivity as demonstrated using an oral glucose tolerance test. Surprisingly, as well as having improved insulin sensitivity, the PTP1B null mice are resistant to diet induced obesity (DIO). This resistance to DIO may suggest that PTP1B has a role in the central regulation of energy balance and work is on going to try to understand further this mechanism. PTP1B has

been shown to be present in the hypothalamus and recent data has suggested that JAK2 is another substrate for PTP1B (Cheng et al, Dev. Cell 2:497-503 (2002). Leptin, a satiety hormone released from the adipocytes, binds to the leptin receptor and induces JAK2 phosphorylation. As with the insulin receptor, JAK2 has a number of substrates. It is thought that PTP1B dephosphorylation of JAK2 may result in changes to the subsequent downstream signalling cascade and may be responsible, at least in part, for the resistance to DIO, in the PTP1B null mice. Accordingly evidence suggests that PTP1B inhibitors are of benefit in the treatment of type 1 or type 2 diabetes, obesity and other conditions which may result from the abnormal regulation of tyrosine phosphatase PTP1B, such as metabolic syndrome (syndrome X), hyperglycemia, hyperinsulinemia, dyslipidemia, polycystic ovarian disease, hypertension, cardiovascular disease (Ukkola and Santaniemi, Journal of Internal Medicine 251:467-475 (2002)).

Compounds which modulate the activity of PTPases are disclosed in International Patent Application, publication number WO 97/40017.

Accordingly there is a continuing need to identify novel compounds which are PTP1B inhibitors. We have found that the compounds defined in the present invention, or pharmaceutically acceptable salts thereof, have surprisingly effective PTP1B inhibitory properties, and accordingly have value in the treatment of disease states mediated by this enzyme.

Accordingly there is provided a compound of formula (I):



(I)

wherein

R_1 is hydrogen, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylthio, halogeno, halogeno(1-6C)alkyl, halogeno(1-6C)alkoxy, halogeno(1-6C)alkylthio, hydroxy(1-6C)alkoxy, dihydroxy(1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy, aryloxy, aryl(1-6C)alkoxy, aryloxy(1-6C)alkoxy, heteroaryl(1-6C)alkoxy, heteroaryloxy, heteroaryloxy(1-6C)alkoxy, (1-6C)alkoxy(1-

6C)alkylthio, (1-6C)alkylthio(1-6C)alkoxy, (1-6C)alkylsulfinyl(1-6C)alkoxy, (1-6C)alkylsulfonyl(1-6C)alkoxy, aryl(1-6C)alkylthio, aryloxy(1-6C)alkylthio, heteroaryl(1-6C)alkylthio, heteroaryloxy(1-6C)alkylthio, (1-6C)alkoxy(1-6C)alkyl, aryloxy(1-6C)alkyl, heteroaryloxy(1-6C)alkyl, (1-6C)alkylthio(1-6C)alkyl, arylthio(1-6C)alkyl, heteroarylthio(1-6C)alkyl, (1-6)alkylsulfinyl(1-6C)alkyl, arylsulfinyl(1-6C)alkyl, (1-6C)alkylsulfonyl(1-6C)alkyl, arylsulfonyl(1-6C)alkyl, carbamoyl(1-6C)alkoxy, carbamoyl(1-6C)alkyl, (2-6C)alkanoylamino(1-6C)alkoxy, (2-6C)alkanoylamino(1-6C)alkyl, aryl(1-6C)alkyl, heteroaryl(1-6C)alkyl, hydroxy(1-6C)alkyl, dihydroxy(2-6C)alkyl, amino(1-6C)alkyl, carboxy(1-6C)alkyl, sulfamoyl(1-6C)alkyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (2-8C)alkenyl, (2-8C)alkynyl, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, *N*-(1-6C)alkylcarbamoyl, *N*,*N*-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, *N*-(1-6C)alkyl-(2-6C)alkanoylamino, *N*-(1-6C)alkylsulphamoyl, *N*,*N*-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and *N*-(1-6C)alkyl-(1-6C)alkanesulphonylamino;

or R_1 is a group of the formula $-Z-(CHR_7)_m-X-NR_8R_9$ wherein

m is 1, 2 or 3;

R_7 is hydrogen, (1-6C)alkyl, aryl, heteroaryl, aryl(1-6C)alkyl, hydroxy or (1-6C)alkoxy;

X is –C(O)-, -S(O)- or $-S(O)_2-$; and R_8 and R_9 are independently selected from hydrogen, (1-6C)alkyl, aryl and heteroaryl; or R_8 and R_9 together with the nitrogen atom to which they are attached form a heterocyclic ring; or X is a covalent bond, R_8 is hydrogen, (1-6C)alkyl or aryl, and R_9 is $-COR_{10}$ or SO_2R_{10} wherein R_{10} is (1-6C)alkyl, aryl, heteroaryl, aryl(1-6C)alkyl or heteroaryl(1-6C)alkyl; and

Z is a covalent bond, O or S; with the proviso that no two heteroatoms are attached through single bonds to the same carbon atom;

R_2 is selected from H, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylthio and halogeno;

or R_1 and R_2 together with the carbon atoms to which they are attached form a 5-7 membered carbocyclic or heterocyclic ring;

R_3 and R_4 are selected such that

(i) R_3 is hydrogen, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylthio or halogeno and R_4 is aryl, biaryl, heteroaryl, (2-6C)alkynyl, (3-7C)cycloalkyl, arylcarbonyl,

heteroarylcarbonyl, aryl(2-6C)alkenyl, aryl(2-6C)alkynyl or heteroaryl(2-6C)alkenyl;

or

(ii) R_4 is hydrogen, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylthio or halogeno and R_3 is aryl, biaryl, heteroaryl, (2-6C)alkynyl, (3-7C)cycloalkyl, arylcarbonyl, heteroarylcarbonyl, aryl(2-6C)alkenyl, aryl(2-6C)alkynyl or heteroaryl(2-6C)alkenyl;

R_5 is hydrogen, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylthio, halo(1-6C)alkyl or halogeno;

R_6 is hydrogen or (1-6C)alkyl;

and wherein any aryl, biaryl or heteroaryl group within or part of the definition of R_1, R_3 or R_4 is unsubstituted or bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, *N*-(1-6C)alkylcarbamoyl, *N*,*N*-di-[(1-6C)alkyl]carbamoyl, *N*-pyrrolidinylcarbonyl, *N*-piperidinylcarbonyl, *N*-(1-6C)alkylcarbamoyloxy(1-6C)alkyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, *N*-(1-6C)alkyl-(2-6C)alkanoylamino, *N*-(1-6C)alkylsulphamoyl, *N*,*N*-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino, *N*-(1-6C)alkyl-(1-6C)alkanesulphonylamino, (1-6C)alkoxy(1-6C)alkyl, (1-6C)alkoxy(1-6C)alkoxy, hydroxy(1-6C)alkyl, carboxy(1-6C)alkyl, aryl(1-6C)alkyl, heteroaryl(1-6C)alkyl, aryloxy(1-6C)alkyl, heteroaryloxy(1-6C)alkyl, aryloxy(1-6C)alkylcarbamoyl, aryloxy(1-6C)alkylsulphamoyl, aryl(1-6C)alkoxy, heteroaryl(1-6C)alkoxy, aryloxy(1-6C)alkoxy, heteroaryloxy(1-6C)alkoxy, aryloxy and heteroaryloxy, and wherein an aryl or heteroaryl moiety of said last twelve groups is unsubstituted or bears 1, 2 or 3 substituents, which may be the same or different; or two adjacent carbons of said aryl, biaryl or heteroaryl group may be linked by a divalent radical of formula $-O(CH_2)_{1-4}O-$;

or a pharmaceutically acceptable salt thereof.

According to a further aspect of the invention there is provided a compound of formula (I), wherein

R_1 is hydrogen, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylthio, halogeno, halogeno(1-6C)alkyl, halogeno(1-6C)alkoxy, halogeno(1-6C)alkylthio, hydroxy(1-6C)alkoxy, dihydroxy(1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy, aryloxy, aryl(1-6C)alkoxy, aryloxy(1-6C)alkoxy, heteroaryl(1-6C)alkoxy, heteroaryloxy(1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkylthio, (1-6C)alkylthio(1-6C)alkoxy, (1-6C)alkylsulfinyl(1-6C)alkoxy, (1-6C)alkylsulfonyl(1-6C)alkoxy, aryl(1-6C)alkylthio, aryloxy(1-6C)alkylthio, heteroaryl(1-6C)alkylthio, heteroaryloxy(1-6C)alkylthio, (1-6C)alkoxy(1-6C)alkyl, aryloxy(1-6C)alkyl, heteroaryloxy(1-6C)alkyl, (1-6C)alkylthio(1-6C)alkyl, arylthio(1-6C)alkyl, heteroarylthio(1-6C)alkyl, (1-6)alkylsulfinyl(1-6C)alkyl, arylsulfinyl(1-6C)alkyl, (1-6C)alkylsulfonyl(1-6C)alkyl, arylsulfonyl(1-6C)alkyl, carbamoyl(1-6C)alkoxy, carbamoyl(1-6C)alkyl, (2-6C)alkanoylamino(1-6C)alkoxy, (2-6C)alkanoylamino(1-6C)alkyl, aryl(1-6C)alkyl, heteroaryl(1-6C)alkyl, hydroxy(1-6C)alkyl, amino(1-6C)alkyl, carboxy(1-6C)alkyl, sulfamoyl(1-6C)alkyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (2-8C)alkenyl, (2-8C)alkynyl, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, *N*-(1-6C)alkylcarbamoyl, *N*,*N*-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, *N*-(1-6C)alkyl-(2-6C)alkanoylamino, *N*-(1-6C)alkylsulphamoyl, *N*,*N*-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and *N*-(1-6C)alkyl-(1-6C)alkanesulphonylamino;

or R_1 is a group of the formula $-Z-(CHR_7)_m-X-NR_8R_9$ wherein

m is 1, 2 or 3;

R_7 is hydrogen, (1-6C)alkyl, aryl, heteroaryl, aryl(1-6C)alkyl, hydroxy or (1-6C)alkoxy;

X is –C(O)-, -S(O)- or $-S(O)_2-$; and R_8 and R_9 are independently selected from hydrogen, (1-6C)alkyl, aryl and heteroaryl; or R_8 and R_9 together with the nitrogen atom to which they are attached form a heterocyclic ring; or X is a covalent bond, R_8 is hydrogen, (1-6C)alkyl or aryl, and R_9 is $-COR_{10}$ or SO_2R_{10} wherein R_{10} is (1-6C)alkyl, aryl, heteroaryl, aryl(1-6C)alkyl or heteroaryl(1-6C)alkyl; and

Z is a covalent bond, O or S; with the proviso that no two heteroatoms are attached through single bonds to the same carbon atom;

R_2 is H or (1-6C)alkyl;

or R_1 and R_2 together with the carbon atoms to which they are attached form a 5-7 membered carbocyclic or heterocyclic ring;

R_3 and R_4 are selected such that

(iii) R_3 is hydrogen, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylthio or halogeno and R_4 is aryl, biaryl, heteroaryl, (3-7C)cycloalkyl, arylcarbonyl, heteroarylcarbonyl, aryl(2-6C)alkenyl or heteroaryl(2-6C)alkenyl;

or

(iv) R_4 is hydrogen, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylthio or halogeno and R_3 is aryl, biaryl, heteroaryl, (3-7C)cycloalkyl, arylcarbonyl, heteroarylcarbonyl, aryl(2-6C)alkenyl or heteroaryl(2-6C)alkenyl;

R_5 is hydrogen, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylthio or halogeno;

R_6 is hydrogen or (1-6C)alkyl;

and wherein any aryl, biaryl or heteroaryl group within or part of the definition of R_1, R_3 or R_4 is unsubstituted or bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, *N*-(1-6C)alkylcarbamoyl, *N*,*N*-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, *N*-(1-6C)alkyl-(2-6C)alkanoylamino, *N*-(1-6C)alkylsulphamoyl, *N*,*N*-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino, *N*-(1-6C)alkyl-(1-6C)alkanesulphonylamino, (1-6C)alkoxy(1-6C)alkyl, (1-6C)alkoxy(1-6C)alkoxy, hydroxy(1-6C)alkyl, aryl(1-6C)alkyl, heteroaryl(1-6C)alkyl, aryloxy(1-6C)alkyl, heteroaryloxy(1-6C)alkyl, aryl(1-6C)alkoxy, heteroaryl(1-6C)alkoxy, aryloxy(1-6C)alkoxy, heteroaryloxy(1-6C)alkoxy, aryloxy and heteroaryloxy, and wherein an aryl or heteroaryl moiety of said last ten groups is unsubstituted or bears 1, 2 or 3 substituents, which may be the same or different; or two adjacent carbons of said aryl, biaryl or heteroaryl group may be linked by a divalent radical of formula $-O(CH_2)_{1-4}O-$;

or a pharmaceutically acceptable salt thereof.

In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups such as propyl, isopropyl and *tert*-butyl, and also (3-7C)cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. However references to individual alkyl groups such as "propyl" are specific for the straight-chain version only, references to individual branched-chain alkyl groups such as

"isopropyl" are specific for the branched-chain version only and references to individual cycloalkyl groups such as "cyclopentyl" are specific for that 5-membered ring only. An analogous convention applies to other generic terms, for example (1-6C)alkoxy includes methoxy, ethoxy, cyclopropyloxy and cyclopentyloxy. Where halogenoalkyl is referred to, this includes mono-, di-, tri- and per-halogenoalkyl. An analogous convention applies to halogenoalkoxy and halogenoalkylthio.

It is to be understood that, insofar as certain of the compounds of Formula (I) defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the above-mentioned activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, the above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

A suitable value for aryl, or for aryl which is part of a value defined herein for R_1 to R_{10} is, for example, a totally unsaturated, mono or bicyclic carbon ring that contains 6-12 atoms. Suitable values for aryl include phenyl or naphthyl, particularly phenyl. A suitable value for biaryl is, for example, biphenyl.

A suitable value for heteroaryl, or for heteroaryl which is part of a value defined herein for R_1 to R_{10} is, for example, a totally unsaturated mono or bicyclic ring containing 5-12 atoms of which at least one atom is chosen from oxygen, sulphur and nitrogen. For example an aromatic 5- or 6-membered monocyclic ring or a 9- or 10-membered bicyclic ring with up to five ring heteroatoms selected from oxygen, nitrogen and sulphur, such as furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazenyl, benzofuranyl, indolyl, benzothienyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, indazolyl, benzofurazanyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalinyl, cinnolinyl or naphthyridinyl.

Suitable values for R_1 to R_{10} or for groups which are part of a value defined herein for R_1 to R_{10}, or for substituents on an aryl or heteroaryl group, include :-

for (1-6C)alkyl:	(1-4C)alkyl, such as methyl, ethyl, propyl, isopropyl and *tert*-butyl; and (1-3C)alkyl, such as methyl, ethyl, propyl and isopropyl;
for (1-6C)alkoxy:	(1-4C)alkoxy, such as methoxy, ethoxy, propoxy, isopropoxy and butoxy; and (1-3C)alkoxy, such as methoxy, ethoxy, propoxy and isopropoxy;
for (1-6C)alkylthio:	(1-4C)alkylthio, such as (1-3C)alkylthio, such as methylthio, ethylthio and propylthio;
for halogeno	fluoro, chloro, bromo and iodo;
for halogeno-(1-6C)alkyl:	halogeno(1-4C)alkyl, such as chloromethyl, 2-chloroethyl, 1-chloroethyl, 3-chloropropyl, fluoromethyl and difluoromethyl;
for halogeno-(1-6C)alkoxy:	halogeno(1-4C)alkoxy, such as chloromethoxy, 2-chloroethoxy, 1-chloroethoxy, 3-chloropropoxy, trifluoromethoxy and 2,2,2-trifluoroethoxy;
for halogeno-(1-6C)alkylthio:	halogeno(1-4C)alkylthio, such as chloromethylthio, 2-chloroethylthio, 1-chloroethylthio and 3-chloropropylthio;
for hydroxy-(1-6C)alkoxy:	hydroxy(1-4C)alkoxy, such as 2-hydroxyethoxy and 3-hydroxypropoxy;
for dihydroxy-(1-6C)alkoxy:	dihydroxy(1-4C)alkoxy, such as 2,3-dihydroxypropoxy;
for (1-6C)alkoxy(1-6C)alkoxy:	(1-4C)alkoxy(1-4C)alkoxy, and (1-3C)alkoxy(1-3C)alkoxy such as methoxymethoxy, 2-methoxyethoxy, ethoxymethoxy and 2-(ethoxy)ethoxy;
for aryl(1-6C)alkoxy:	aryl(1-4C)alkoxy, such as benzyloxy, 1-phenylethoxy, 2-phenylethoxy, 3-phenylpropoxy, 1-

naphthylmethoxy, 2-naphthylmethoxy, 2-(1-naphthyl)ethoxy, 2-(2-naphthyl)ethoxy, 3-(1-naphthyl)propoxy and 3-(2-naphthyl)propoxy

for aryloxy(1-6C)alkoxy: aryloxy(1-4C)alkoxy, such as phenoxymethoxy, phenoxyethoxy, phenoxypropoxy, 1-naphthylmethoxy, 2-naphthylmethoxy, 2-(1-naphthyl)ethoxy, 2-(2-naphthyl)ethoxy, 3-(1-naphthyl)propoxy and 2-(2-naphthyl)propoxy;

for (1-6C)alkoxy-(1-6C)alkylthio: (1-4C)alkoxy(1-4C)alkylthio, such as methoxymethylthio, ethoxymethylthio, 1-methoxyethylthio, 2-methoxyethylthio, 2-ethoxyethylthio and 3-methoxypropylthio;

(1-6C)alkylthio(1-6C)alkoxy: (1-4C)alkylthio(1-4C)alkoxy, such as methylthiomethoxy, 2-(methylthio)ethoxy, ethylthiomethoxy and 2-(ethylthio)ethoxy;

(1-6C)alkylsulfinyl(1-6C)alkoxy: (1-4C)alkylsulfinyl(1-4C)alkoxy, such as methylsulfinylmethoxy, 2-(methylsulfinyl)ethoxy, ethylsulfinylmethoxy and 2-(ethylsulfinyl)ethoxy;

(1-6C)alkylsulfonyl(1-6C)alkoxy methylsulfonylmethoxy, 2-(methylsulfonyl)ethoxy, ethylsulfonylmethoxy and 2-(ethylsulfonyl)ethoxy;

for aryl(1-6C)alkylthio: aryl(1-4C)alkylthio, such as phenylmethylthio, 2-phenylethylthio, 3-phenylpropylthio, 1-naphthylmethylthio and 2-naphthylmethylthio;

for aryloxy(1-6C)alkylthio: aryloxy(1-4C)alkylthio, such as phenoxymethylthio, 2-phenoxyethylthio, 3-phenoxypropylthio, 1-naphthyloxymethylthio and 2-naphthyloxymethylthio;

for (1-6C)alkoxy-(1-6C)alkyl: (1-4C)alkoxy(1-4C)alkyl, and (1-3C)alkoxy(1-3C)alkyl, such as methoxymethyl, ethoxymethyl, 1-methoxyethyl,2-methoxyethyl, 2-ethoxyethyl and 3-methoxypropyl;

for aryloxy(1-6C)alkyl: aryloxy(1-4C)alkyl, such as phenoxymethyl, 1-phenoxyethyl, 2-phenoxyethyl and 3-phenoxypropyl;

for aryloxy(1-6C)alkylcarbamoyl: aryloxy(1-4C)alkylcarbamoyl, such as phenoxymethylcarbamoyl, 1-phenoxyethylcarbamoyl, 2-phenoxyethylcarbamoyl and 3-phenoxypropylcarbamoyl;

for aryloxy(1-6C)alkylsulphamoyl: aryloxy(1-4C)alkylsulphamoyl, such as phenoxymethylsulphamoyl, 1-phenoxyethylsulphamoyl, 2-phenoxyethylsulphamoyl and 3-phenoxypropylsulphamoyl;

for (1-6C)alkylthio(1-6C)alkyl: (1-4C)alkylthio(1-4C)alkyl, such as methylthiomethyl, 2-(methylthio)ethyl, ethylthiomethyl and 2-(ethylthio)ethyl;

for arylthio(1-6C)alkyl: arylthio(1-4C)alkyl, such as phenylthiomethyl, 1-phenylthioethyl, 2-phenylthioethyl and 3-phenylthiopropyl;

for (1-6C)alkylsulfinyl(1-6C)alkyl: (1-4C)alkylsulfinyl(1-4C)alkyl, such as methylsulfinylmethyl, 2-(methylsulfinyl)ethyl

for arylsulfinyl(1-6C)alkyl: arylsulfinyl(1-4C)alkyl, such as phenylsulfinylmethyl, 2-(phenylsulfinyl)ethyl, 1-naphthylsulfinylmethyl, 2-(1-naphthylsulfinyl)ethyl;

for (1-6C)alkylsulfonyl(1-6C)alkyl: (1-4C)alkylsulfonyl(1-4C)alkyl, such as methylsulfonylmethyl, 2-(methylsulfonyl)ethyl

for arylsulfonyl(1-6C)alkyl: arylsulfonyl(1-4C)alkyl, such as phenylsulfonylmethyl, 2-(phenylsulfonyl)ethyl

carbamoyl(1-6C)alkoxy: carbamoylmethoxy, 2-(carbamoyl)ethoxy, 3-(carbamoyl)propoxy

carbamoyl(1-6C)alkyl: carbamoyl(1-4C)alkyl, such as carbamoylmethyl, 2-(carbamoyl)ethyl, 3-(carbamoyl)propyl

carbamoyl(1-6C)alkoxy: carbamoyl(1-4C)alkoxy, such as carbamoylmethoxy, 2-(carbamoyl)ethoxy, 3-(carbamoyl)propoxy

(2-6C)alkanoylamino(1-6C)alkoxy:	(2-4C)alkanoylamino(1-6C)alkoxy, such as acetamidomethoxy, propionamidomethoxy and 2-acetamidoethoxy;
for (2-6C)alkanoylamino-(1-6C)alkyl:	(2-4C)alkanoylamino(1-4C)lkyl, such as acetamidomethyl, propionamidomethyl and 2-acetamidoethyl;
for aryl(1-6C)alkyl:	aryl(1-4C)alkyl, such as benzyl, 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl, 1-naphthylmethyl, 2-naphthylmethyl, 2-(1-naphthyl)ethyl, 2-(2-naphthyl)ethyl, 3-(1-naphthyl)propyl and 3-(2-naphthyl)propyl;
for aryl(2-6C)alkenyl:	aryl(2-4C)alkenyl, such as cis- or trans-styryl;
for aryl(2-6C)alkynyl:	aryl(2-4C)alkylnyl, such as phenylethynyl and 3-phenylpropyn-1-yl;
for hydroxy(1-6C)alkyl:	hydroxy(1-4C)alkyl, and hydroxy(1-3C)alkyl such as hydroxymethyl, 2-hydroxyethyl and 3-hydroxypropyl;
for dihydroxy(2-6C)alkyl:	dihydroxy(2-4C)alkyl, such as 1,2-dihydroxyethyl and 1,3-dihydroxypropyl;
for amino(1-6C)alkyl:	amino(1-4C)alkyl, such as aminomethyl, 2-aminoethyl and 3-aminopropyl;
for carboxy(1-6C)alkyl:	carboxy(1-4C)alkyl, such as carboxymethyl, 2-carboxyethyl and 3-carboxypropyl;
for sulfamoyl(1-6C)alkyl:	sulfamoyl(1-4C)alkyl, such as sulfamoylmethyl, 2-sulfamoylethyl and 3-sulfamoylpropyl;
for (2-8C)alkenyl:	(2-6C)alkenyl, such as (2-4C)alkenyl, such as vinyl, isopropenyl, allyl and but-2-enyl;
for (2-8C)alkynyl:	(2-6C)alkynyl, such as (2-4C)alkynyl, such as ethynyl, 2-propynyl and but-2-ynyl;
for (2-6C)alkenyloxy:	(2-4C)alkenyloxy, such as vinyloxy and allyloxy;
for (2-6C)alkynyloxy:	(2-4C)alkynyloxy, such as ethynyloxy and 2-propynyloxy;

for (1-6C)alkylsulfinyl: (1-4C)alkylsulfinyl, such as (1-3C)alkylsulfinyl, such as methylsulfinyl and ethylsulfinyl;

for (1-6C)alkylsulfonyl: (1-4C)alkylsulfonyl, such as (1-3C)alkylsulfonyl, such as methylsulfonyl and ethylsulfonyl;

for (1-6C)alkylamino: (1-4C)alkylamino, such as methylamino, ethylamino, propylamino, isopropylamino and butylamino;

for di-[(1-6C)alkyl]amino: di-[(1-4C)alkyl]amino, such as dimethylamino, diethylamino, *N*-ethyl-*N*-methylamino and diisopropylamino;

for (1-6C)alkoxycarbonyl: (1-4C)alkoxycarbonyl, such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and *tert*-butoxycarbonyl; and (1-3C)alkoxycarbonyl, such as methoxycarbonyl, ethoxycarbonyl and propoxycarbonyl;

for *N*-(1-6C)alkylcarbamoyl: *N*-(1-4C)alkylcarbamoyl, such as *N*-(1-3C)alkylcarbamoyl, such as *N*-methylcarbamoyl, *N*-ethylcarbamoyl and *N*-propylcarbamoyl;

for *N*,*N*-di-[(1-6C)alkyl]carbamoyl: *N*,*N*-di-[(1-4C)alkyl]carbamoyl, such as *N*,*N*-di-[(1-3C)alkyl]carbamoyl, such as *N*,*N*-dimethylcarbamoyl, *N*-ethyl-*N*-methylcarbamoyl and *N*,*N*-diethylcarbamoyl;

for *N*-(1-6C)alkylcarbamoyloxy(1-6C)alkyl: *N*-(1-4C)alkylcarbamoyloxy(1-4C)alkyl, such as *N*-tert-butylcarbamoyloxymethyl;

for (2-6C)alkanoyl: (2-4C)alkanoyl, such as acetyl and propionyl;

for (2-6C)alkanoyloxy: (2-4C)alkanoyloxy, such as acetoxy and propionyloxy;

for (2-6C)alkanoylamino: (2-4C)alkanoylamino, such as acetamido and propionamido;

for *N*-(1-6C)alkyl-(2-6C)alkanoylamino: *N*-(1-4C)alkyl-(2-4C)alkanoylamino, such as *N*-(1-3C)alkyl-(2-4C)alkanoylamino, such as *N*-methylacetamido and *N*-methylpropionamido;

for *N*-(1-6C)alkylsulfamoyl:	*N*-(1-4C)alkylsulfamoyl, such as *N*-(1-3C)alkylsulfamoyl, such as *N*-methylsulfamoyl and *N*-ethylsulphamoyl;
for *N,N*-di-[(1-6C)alkyl]sulfamoyl:	*N,N*-di-[(1-4C)alkyl]sulfamoyl, such as *N,N*-di-[(1-3C)alkyl]sulfamoyl, such as *N,N*-dimethylsulfamoyl;
for (1-6C)alkanesulfonylamino:	(1-4C)alkanesulfonylamino, such as (1-3C)alkanesulfonylamino, such as methanesulfonylamino and ethanesulfonylamino;
for *N*-(1-6C)alkyl-(1-6C)alkanesulfonylamino:	*N*-(1-4C)alkyl-(1-4C)alkanesulfonylamino, such as *N*-(1-3C)alkyl-(1-3C)alkanesulfonylamino, such as *N*-methylmethanesulfonylamino and *N*-methylethanesulfonylamino;

A suitable value for a divalent radical of formula $-O(CH_2)_{1-4}O-$ includes, for example, methylenedioxy and ethylenedioxy.

A suitable value for R_8 and R_9 when, together with the nitrogen atom to which they are attached, they form a heterocyclic ring includes, for example, a saturated or partially saturated heterocyclic ring optionally substituted with a (1-6C)alkyl group, such as pyrrolidino, piperidino, morpholino, thiomorpholino, piperazino or *N*-methylpiperazino.

A suitable value for R_1 and R_2 when, together with the carbon atoms to which they are attached, they form a 5-7 membered carbocyclic or heterocyclic ring, includes for example when they form a 5, 6 or 7-membered partially saturated or unsaturated ring containing 0, 1, 2 or 3 oxygen, sulphur or nitrogen atoms. To form the 5-7 membered ring, R_1 together with R_2 is a diradical, including for example, $-CH_2CH_2CH_2-$, $-CH_2-CH=CH-$, $-CH=CH-CH_2$, $-CH_2CH_2CH_2CH_2-$, $-CH=CH-CH=CH-$, $-CH_2CH_2-CH=CH-$, $-CH=CH-CH_2CH_2-$ or $-CH_2CH_2CH_2CH_2CH_2-$, wherein a CH_2 group may be replaced by an O, S or NH moiety, for example as in a $-O-(CH_2)_{1-4}O-$ diradical (such as a methylenedioxy group), or –CH= or =CH- may be replaced by –N= or =N- respectively.

In one aspect, when any aryl, biaryl or heteroaryl group within or part of the definition of R_1, R_3 or R_4 bears 1, 2 or 3 substituents, which may be the same or different, said

substituents are independently selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkoxycarbonyl, *N*-(1-6C)alkylcarbamoyl, *N*,*N*-di-[(1-6C)alkyl]carbamoyl, *N*-pyrrolidinylcarbonyl, *N*-piperidinylcarbonyl, *N*-(1-6C)alkylcarbamoyloxy(1-6C)alkyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, *N*-(1-6C)alkylsulphamoyl, (1-6C)alkoxy(1-6C)alkyl, (1-6C)alkoxy(1-6C)alkoxy, hydroxy(1-6C)alkyl, carboxy(1-6C)alkyl, aryloxy(1-6C)alkyl, heteroaryloxy(1-6C)alkyl, aryloxy(1-6C)alkylcarbamoyl, aryloxy(1-6C)alkylsulphamoyl, aryl(1-6C)alkoxy, heteroaryl(1-6C)alkoxy, aryloxy(1-6C)alkoxy, heteroaryloxy(1-6C)alkoxy, aryloxy and heteroaryloxy, and wherein an aryl or heteroaryl moiety of said last ten groups is unsubstituted or bears 1, 2 or 3 substituents, which may be the same or different; or two adjacent carbons of said aryl, biaryl or heteroaryl group may be linked by a divalent radical of formula $-O(CH_2)_{1-4}O-$.

In another aspect, when any aryl, biaryl or heteroaryl group within or part of the definition of R_1, R_3 or R_4 bears 1, 2 or 3 substituents, which may be the same or different, said substituents are independently selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkoxycarbonyl, *N*-(1-6C)alkylcarbamoyl, *N*,*N*-di-[(1-6C)alkyl]carbamoyl, *N*-pyrrolidinylcarbonyl, *N*-piperidinylcarbonyl, *N*-(1-6C)alkylcarbamoyloxy(1-6C)alkyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, (1-6C)alkoxy(1-6C)alkyl, (1-6C)alkoxy(1-6C)alkoxy, hydroxy(1-6C)alkyl, carboxy(1-6C)alkyl, aryloxy(1-6C)alkyl, heteroaryloxy(1-6C)alkyl, aryloxy(1-6C)alkylcarbamoyl, aryloxy(1-6C)alkylsulphamoyl, aryl(1-6C)alkoxy, heteroaryl(1-6C)alkoxy, aryloxy(1-6C)alkoxy, heteroaryloxy(1-6C)alkoxy, aryloxy and heteroaryloxy, and wherein an aryl or heteroaryl moiety of said last ten groups is unsubstituted or bears 1, 2 or 3 substituents, which may be the same or different; or two adjacent carbons of said aryl, biaryl or heteroaryl group may be linked by a divalent radical of formula $-O(CH_2)_{1-4}O-$.

In another aspect, when any aryl, biaryl or heteroaryl group within or part of the definition of R_1, R_3 or R_4 bears 1, 2 or 3 substituents, which may be the same or different, said substituents are independently selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (1-6C)alkoxy, (1-6C)alkylthio, *N*,*N*-di-[(1-6C)alkyl]carbamoyl, *N*-pyrrolidinylcarbonyl, *N*-piperidinylcarbonyl,

N-(1-6C)alkylcarbamoyloxy(1-6C)alkyl, (2-6C)alkanoyl, (2-6C)alkanoylamino, (1-6C)alkoxy(1-6C)alkyl, carboxy(1-6C)alkyl, aryloxy(1-6C)alkyl, aryloxy(1-6C)alkylcarbamoyl, aryloxy(1-6C)alkylsulphamoyl, aryl(1-6C)alkoxy and aryloxy(1-6C)alkoxy, and wherein an aryl or heteroaryl moiety of said last five groups is unsubstituted or bears 1 or 2 substituents, which may be the same or different; or two adjacent carbons of said aryl, biaryl or heteroaryl group may be linked by a divalent radical of formula $-O(CH_2)_{1-4}O-$.

In another aspect, when any aryl, biaryl or heteroaryl group within or part of the definition of R_1, R_3 or R_4 bears 1, 2 or 3 substituents, which may be the same or different, said substituents are independently selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, carboxy, carbamoyl, (1-4C)alkyl, (2-4C)alkenyl, (1-4C)alkoxy, (1-4C)alkylthio, *N*,*N*-di-[(1-4C)alkyl]carbamoyl, *N*-pyrrolidinylcarbonyl, *N*-piperidinylcarbonyl, *N*-(1-4C)alkylcarbamoyloxy(1-4C)alkyl, (2-4C)alkanoyl, (2-4C)alkanoylamino, (1-4)alkoxy(1-4C)alkyl, carboxy(1-4C)alkyl, aryloxy(1-4C)alkyl, aryloxy(1-6C)alkylcarbamoyl, aryloxy(1-6C)alkylsulphamoyl, aryl(1-6C)alkoxy and aryloxy(1-6C)alkoxy, and wherein an aryl or heteroaryl moiety of said last five groups is unsubstituted or bears 1 or 2 substituents, which may be the same or different; or two adjacent carbons of said aryl, biaryl or heteroaryl group may be linked by a divalent radical of formula $-O(CH_2)_{1-4}O-$.

Suitable values for optional substituents on an aryl or heteroaryl moiety of an aryl(1-6C)alkyl, heteroaryl(1-6C)alkyl, aryloxy(1-6C)alkyl, heteroaryloxy(1-6C)alkyl, aryl(1-6C)alkoxy, heteroaryl(1-6C)alkoxy, aryloxy(1-6C)alkoxy, heteroaryloxy(1-6C)alkoxy, aryloxy(1-6C)alkylcarbamoyl, aryloxy(1-6C)alkylsulphamoyl, aryloxy or heteroaryloxy substituent include, for example, halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, *N*-(1-6C)alkylcarbamoyl, *N*,*N*-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, *N*-(1-6C)alkyl-(2-6C)alkanoylamino, *N*-(1-6C)alkylsulfamoyl, *N*,*N*-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulfonylamino, *N*-(1-6C)alkyl-(1-6C)alkanesulfonylamino, (1-6C)alkoxy(1-6C)alkyl, (1-6C)alkoxy(1-6C)alkoxy and hydroxy(1-6C)alkyl.

Further suitable values for optional substituents on an aryl or heteroaryl moiety of an aryl(1-6C)alkyl, heteroaryl(1-6C)alkyl, aryloxy(1-6C)alkyl, heteroaryloxy(1-6C)alkyl,

aryl(1-6C)alkoxy, heteroaryl(1-6C)alkoxy, aryloxy(1-6C)alkoxy, heteroaryloxy(1-6C)alkoxy, aryloxy(1-6C)alkylcarbamoyl, aryloxy(1-6C)alkylsulphamoyl, aryloxy or heteroaryloxy substituent include, for example, halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, *N*-(1-6C)alkylcarbamoyl, *N,N*-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, *N*-(1-6C)alkyl-(2-6C)alkanoylamino, *N*-(1-6C)alkylsulfamoyl, *N,N*-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulfonylamino, *N*-(1-6C)alkyl-(1-6C)alkanesulfonylamino, (1-6C)alkoxy(1-6C)alkyl, (1-6C)alkoxy(1-6C)alkoxy and hydroxy(1-6C)alkyl.

Still further suitable values for optional substituents on an aryl or heteroaryl moiety of an aryl(1-6C)alkyl, heteroaryl(1-6C)alkyl, aryloxy(1-6C)alkyl, heteroaryloxy(1-6C)alkyl, aryl(1-6C)alkoxy, heteroaryl(1-6C)alkoxy, aryloxy(1-6C)alkoxy, heteroaryloxy(1-6C)alkoxy, aryloxy(1-6C)alkylcarbamoyl, aryloxy(1-6C)alkylsulphamoyl, aryloxy or heteroaryloxy substituent include, for example, halogeno, trifluoromethyl, cyano, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkoxycarbonyl, (1-6C)alkoxy(1-6C)alkyl, (1-6C)alkoxy(1-6C)alkoxy and hydroxy(1-6C)alkyl.

Still further suitable values for optional substituents on an aryl or heteroaryl moiety of an aryl(1-6C)alkyl, heteroaryl(1-6C)alkyl, aryloxy(1-6C)alkyl, heteroaryloxy(1-6C)alkyl, aryl(1-6C)alkoxy, heteroaryl(1-6C)alkoxy, aryloxy(1-6C)alkoxy, heteroaryloxy(1-6C)alkoxy, aryloxy(1-6C)alkylcarbamoyl, aryloxy(1-6C)alkylsulphamoyl, aryloxy or heteroaryloxy substituent include, for example, halogeno, trifluoromethyl, cyano, hydroxy, amino, carboxy, carbamoyl, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylsulfonyl, (1-4C)alkoxycarbonyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkoxy and hydroxy(1-4C)alkyl.

Still further suitable values for optional substituents on an aryl or heteroaryl moiety of an aryl(1-6C)alkyl, heteroaryl(1-6C)alkyl, aryloxy(1-6C)alkyl, heteroaryloxy(1-6C)alkyl, aryl(1-6C)alkoxy, heteroaryl(1-6C)alkoxy, aryloxy(1-6C)alkoxy, heteroaryloxy(1-6C)alkoxy, aryloxy(1-6C)alkylcarbamoyl, aryloxy(1-6C)alkylsulphamoyl, aryloxy or heteroaryloxy substituent include, for example, halogeno, hydroxy, carboxy, carbamoyl, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylsulfonyl, (1-4C)alkoxycarbonyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkoxy and hydroxy(1-4C)alkyl.

Still further suitable values for optional substituents on an aryl or heteroaryl moiety of an aryl(1-6C)alkyl, heteroaryl(1-6C)alkyl, aryloxy(1-6C)alkyl, heteroaryloxy(1-6C)alkyl, aryl(1-6C)alkoxy, heteroaryl(1-6C)alkoxy, aryloxy(1-6C)alkoxy, heteroaryloxy(1-6C)alkoxy, aryloxy(1-6C)alkylcarbamoyl, aryloxy(1-6C)alkylsulphamoyl, aryloxy or heteroaryloxy substituent include, for example, halogeno, cyano, nitro, hydroxy, carboxy, carbamoyl, (1-3C)alkyl, (2-4C)alkenyl), (2-4C)alkynyl, (1-3C)alkoxy, (2-4C)alkenyloxy, (2-4C)alkynyloxy, (1-3C)alkylthio, (1-3C)alkylsulfinyl, (1-3C)alkylsulfonyl, (1-6C)alkoxycarbonyl, *N*-(1-3C)alkylcarbamoyl, *N,N*-di-[(1-3C)alkyl]carbamoyl, (2-4C)alkanoyl, (2-4C)alkanoyloxy, (2-4C)alkanoylamino, *N*-(1-3C)alkyl-(2-4C)alkanoylamino, *N*-(1-3C)alkylsulfamoyl, *N,N*-di-[(1-3C)alkyl]sulfamoyl, (1-3C)alkanesulfonylamino, *N*-(1-3C)alkyl-(1-3C)alkanesulfonylamino, (1-3C)alkoxy(1-3C)alkyl, (1-3C)alkoxy(1-3C)alkoxy and hydroxy(1-3C)alkyl.

Still further suitable values for optional substituents on an aryl or heteroaryl moiety of an aryl(1-6C)alkyl, heteroaryl(1-6C)alkyl, aryloxy(1-6C)alkyl, heteroaryloxy(1-6C)alkyl, aryl(1-6C)alkoxy, heteroaryl(1-6C)alkoxy, aryloxy(1-6C)alkoxy, heteroaryloxy(1-6C)alkoxy, aryloxy(1-6C)alkylcarbamoyl, aryloxy(1-6C)alkylsulphamoyl, aryloxy or heteroaryloxy substituent include, for example, halogeno, hydroxy, carboxy, carbamoyl, (1-3C)alkyl, (1-3C)alkoxy, (1-3C)alkylsulfonyl, (1-3C)alkoxycarbonyl, (1-3C)alkoxy(1-3C)alkyl, (1-3C)alkoxy(1-3C)alkoxy and hydroxy(1-3C)alkyl.

A suitable pharmaceutically acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically acceptable salt of a compound of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

The invention relates to any and all tautomeric forms of the compounds of the formula (I) that possess PTP1B inhibitory activity.

It is also to be understood that certain compounds of the formula (I) may exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which possess PTP1B inhibitory activity.

Particular values of variable groups are as follows. Such values may be used where appropriate with any of the other values, definitions, claims or embodiments defined hereinbefore or hereinafter.

(1) R_1 is hydrogen

(2) R_1 has any of the values defined herein other than hydrogen

(3) R_5 is hydrogen and R_1 has any of the values defined herein other than hydrogen

(4) R_5 is hydrogen and R_1 is (1-6C)alkoxy, such as (1-4C)alkoxy, for example methoxy

(5) R_5 is hydrogen and R_1 is hydroxy-(1-6C)alkoxy, such as hydroxy(1-4C)alkoxy, for example, 2-hydroxyethoxy

(6) R_5 is hydrogen and R_1 is (1-6C)alkoxy(1-6C)alkoxy, such as (1-4C)alkoxy(1-4C)alkoxy, for example. 2-methoxyethoxy

(7) R_5 is hydrogen and R_1 is (1-6C)alkylthio(1-6C)alkoxy, such as (1-4C)alkylthio(1-4C)alkoxy, for example, 2-(methylthio)ethoxy

(8) R_5 is hydrogen and R_1 is (1-6C)alkylsulfinyl(1-6C)alkoxy, such as (1-4C)alkylsulfinyl(1-4C)alkoxy, for example, 2-(methylsulfinyl)ethoxy

(9) R_5 is hydrogen and R_1 is (1-6C)alkylsulfonyl(1-6C)alkoxy, such as (1-4C)alkylsulfonyl(1-4C)alkoxy, for example, 2-(methylsulfonyl)ethoxy

(10) R_5 is hydrogen and R_1 is aryl(1-6C)alkoxy, such as aryl(1-4C)alkoxy, for example, benzyloxy or phenethyloxy

(11) R_5 is hydrogen and R_1 is fluoro(1-6C)alkoxy, such as fluoro(1-4C)alkoxy, for example trifluoromethoxy or 2,2,2-trifluoroethoxy

(12) R_5 is hydrogen and R_1 is carbamoyl(1-6C)alkoxy, such as carbamoyl(1-4C)alkoxy, for example, carbamoylmethoxy or 2-carbamoylethoxy

(13) R_5 is hydrogen and R_1 is (2-6C)alkanoylamino(1-6C)alkoxy, such as (2-4C)alkanoylamino(1-4C)alkoxy, for example acetamidomethoxy

(14) R_5 is hydrogen and R_1 is (1-6C)alkoxy-(1-6C)alkyl, such as (1-4C)alkoxy-(1-4C)alkyl, for example, 2-methoxyethyl

(15) R_5 is hydrogen and R_1 is aryloxy(1-6C)alkyl, such as aryloxy(1-4C)alkyl, for example, phenyloxymethyl or 2-(phenyloxy)ethyl

(16) R_5 is hydrogen and R_1 is (1-6C)alkylsulfinyl(1-6C)alkyl, such as (1-4C)alkylsulfinyl(1-4C)alkyl, for example, methylsulfinylmethyl or 2-(methylsulfinyl)ethyl

(17) R_5 is hydrogen and R_1 is (1-6C)alkylsulfonyl(1-6C)alkyl, such as (1-4C)alkylsulfonyl(1-4C)alkyl, for example, methylsulfonylmethyl or 2-(methylsulfonyl)ethyl

(18) R_5 is hydrogen and R_1 is (2-6C)alkanoylamino(1-6C)alkyl, such as (2-4C)alkanoylamino(1-4C)alkyl, for example, acetylaminomethyl or 2-(acetylamino)ethyl

(19) R_5 is hydrogen and R_1 is carbamoyl(1-6C)alkyl, such as carbamoyl(1-4C)alkyl, for example, carbamoylmethyl or 2-carbamoylethyl

(20) R_2 is hydrogen

(21) R_2 is hydrogen or (1-6C)alkyl

(22) R_4 is hydrogen and R_3 is unsubstituted or substituted aryl

(23) R_4 is hydrogen and R_3 is unsubstituted aryl or aryl bearing 1, 2 or 3 substituents independently selected from (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylthio, halogeno, (2-4C)alkanoylaminophenoxy, cyano, nitro, hydroxy, trifluoromethyl, (2-4C)alkanoyl, carboxy, carboxy(1-4C)alkyl, hydroxymethyl, benzyloxy, (1-4C)alkoxy(1-4C)alkyl, amino and *N*,*N*-(1-4C)dialkylamino

(24) R_4 is hydrogen and R_3 is unsubstituted aryl or aryl bearing 1, 2 or 3 substituents independently selected from (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylthio, halogeno, (2-4C)alkanoylamino, *N*-tert-butylcarbamoyloxymethyl, phenoxy, cyano, nitro, hydroxy, trifluoromethyl, (2-4C)alkanoyl, carboxy, carboxy(1-4C)alkyl, hydroxymethyl, benzyloxy, (1-4C)alkoxy(1-4C)alkyl, amino, *N*,*N*-(1-4C)dialkylamino, *N*-pyrrolidinylcarbonyl and *N*-piperidinylcarbonyl

(25) R_4 is hydrogen and R_3 is aryl bearing 1 substituent independently selected from (i) aryl(1-6C)alkyl; (ii) aryloxy(1-6C)alkyl; (iii) aryl(1-6C)alkoxy; (iv) aryloxy(1-6C)alkoxy; (v) aryloxy; (vi) aryloxy(1-6C)alkylcarbamoyl; and (vii) aryloxy(1-6C)alkylsulfamoyl; wherein the aryl moiety of groups (i) to (vii) is unsubstituted or is substituted with 1, 2 or 3 substituents independently selected from any of the values defined hereinbefore or hereinafter as suitable values for such substituents; each of the groups (i) to (vii) may be selected independently and used where appropriate with any of the other values, definitions, claims or embodiments defined hereinbefore or hereinafter

(26) R_4 is hydrogen and R_3 is aryl bearing 1 substituent selected from (i) aryl(1-6C)alkyl; (ii) aryloxy(1-6C)alkyl; (iii) aryl(1-6C)alkoxy; (iv) aryloxy(1-6C)alkoxy; (v) aryloxy; (vi) aryloxy(1-6C)alkylcarbamoyl; and (vii) aryloxy(1-6C)alkylsulfamoyl;

wherein the aryl moiety of groups (i) to (vii) is an aryl group bearing a 3-hydroxy and a 2-carboxy or 2-(1-4C)alkoxycarbonyl group; each of the groups (i) to (vii) may be selected independently and used where appropriate with any of the other values, definitions, claims or embodiments defined hereinbefore or hereinafter

(27) R_4 is hydrogen and R_3 is unsubstituted or substituted biaryl

(28) R_4 is hydrogen and R_3 is unsubstituted or substituted heteroaryl

(29) R_4 is hydrogen and R_3 is (3-7C)cycloalkyl

(30) R_4 is hydrogen and R_3 is unsubstituted or substituted arylcarbonyl

(31) R_4 is hydrogen and R_3 is unsubstituted or substituted heteroarylcarbonyl

(32) R_4 is hydrogen and R_3 is unsubstituted or substituted aryl(2-6C)alkenyl

(33) R_4 is hydrogen and R_3 is unsubstituted or substituted aryl(2-6C)alkynyl

(34) R_4 is hydrogen and R_3 is unsubstituted or substituted heteroaryl(2-6C)alkenyl

(35) R_3 is hydrogen and R_4 is unsubstituted or substituted aryl

(36) R_3 is hydrogen and R_4 is unsubstituted aryl or aryl bearing 1, 2 or 3 substituents, which may be the same or different, selected from (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylthio, halogeno, (2-4C)alkanoylamino, phenoxy, cyano, nitro, hydroxy, trifluoromethyl, (2-4C)alkanoyl, carboxy, hydroxymethyl, benzyloxy, (1-4C)alkoxy(1-4C)alkyl, amino and *N*,*N*-(1-4C)dialkylamino

(37) R_3 is hydrogen and R_4 is unsubstituted aryl or aryl bearing 1, 2 or 3 substituents, which may be the same or different, selected from (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylthio, halogeno, (2-4C)alkanoylamino, *N*-tert-butylcarbamoyloxymethyl, phenoxy, cyano, nitro, hydroxy, trifluoromethyl, (2-4C)alkanoyl, carboxy, carboxy(1-4C)alkyl, hydroxymethyl, benzyloxy, (1-4C)alkoxy(1-4C)alkyl, amino, *N*,*N*-(1-4C)dialkylamino, *N*-pyrrolidinylcarbonyl and *N*-piperidinylcarbonyl

(38) R_3 is hydrogen and R_4 is aryl bearing 1 substituent independently selected from (i) aryl(1-6C)alkyl; (ii) aryloxy(1-6C)alkyl; (iii) aryl(1-6C)alkoxy; (iv) aryloxy(1-6C)alkoxy; (v) aryloxy; (vi) aryloxy(1-6C)alkylcarbamoyl; and (vii) aryloxy(1-6C)alkylsulfamoyl; wherein the aryl moiety of groups (i) to (vii) is unsubstituted or is substituted with 1, 2 or 3 substituents independently selected from any of the values defined hereinbefore or hereinafter as suitable values for such substituents; each of the groups (i) to (vii) may be selected independently and used where appropriate with any of the other values, definitions, claims or embodiments defined hereinbefore or hereinafter

(39) R_3 is hydrogen and R_4 is aryl bearing 1 substituent independently selected from

(i) aryl(1-6C)alkyl; (ii) aryloxy(1-6C)alkyl; (iii) aryl(1-6C)alkoxy; (iv) aryloxy(1-6C)alkoxy; (v) aryloxy; (vi) aryloxy(1-6C)alkylcarbamoyl; and (vii) aryloxy(1-6C)alkylsulfamoyl; wherein the aryl moiety of groups (i) to (vii) is an aryl group bearing a 3-hydroxy and a 2-carboxy or 2-(1-4C)alkoxycarbonyl group; each of the groups (i) to (vii) may be selected independently and used where appropriate with any of the other values, definitions, claims or embodiments defined hereinbefore or hereinafter

(40) R_3 is hydrogen and R_4 is unsubstituted or substituted biaryl

(41) R_3 is hydrogen and R_4 is unsubstituted or substituted heteroaryl

(42) R_3 is hydrogen and R_4 is (3-7C)cycloalkyl

(43) R_3 is hydrogen and R_4 is unsubstituted or substituted arylcarbonyl

(44) R_3 is hydrogen and R_4 is unsubstituted or substituted heteroarylcarbonyl

(45) R_3 is hydrogen and R_4 is unsubstituted or substituted aryl(2-6C)alkenyl

(46) R_3 is hydrogen and R_4 is unsubstituted or substituted aryl(2-6C)alkynyl

(47) R_3 is hydrogen and R_4 is unsubstituted or substituted heteroaryl(2-6C)alkenyl

(48) R_6 is hydrogen

(49) R_7 is hydrogen

(50) R_8 is hydrogen

(51) R_8 is (1-4C)alkyl

(52) R_9 is –C(O)(1-4C)alkyl

(53) R_9 is $-S(O)_2$(1-4C)alkyl

(54) X is –C(O)-

(55) m is the integer 1

(56) m is the integer 2

(57) m is the integer 3

(58) Z is a covalent bond

(59) Z is –O-

In another aspect of the invention, there is provided a compound of the formula I, or a pharmaceutically acceptable salt thereof, wherein R_1 has any of the values defined above, R_2, R_5 and R_6 are each hydrogen, R_3 is unsubstituted aryl or aryl bearing 1, 2 or 3 substituents having any of the values defined above; and R_4 is H, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylthio or halogeno.

In another aspect of the invention, there is provided a compound of the formula I, or a pharmaceutically acceptable salt thereof, as defined herein, wherein R_1 has any of the values defined above other than hydrogen.

In another aspect of the invention, there provided a compound of the formula I, or a pharmaceutically acceptable salt thereof, wherein R_1 is (1-6C)alkoxy, hydroxy-(1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy, (1-6C)alkylthio(1-6C)alkoxy, (1-6C)alkylsulfinyl(1-6C)alkoxy, (1-6C)alkylsulfonyl(1-6C)alkoxy, aryl(1-6C)alkoxy, fluoro(1-6C)alkoxy, carbamoyl(1-6C)alkoxy, (2-6C)alkanoylamino(1-6C)alkoxy, (1-6C)alkoxy-(1-6C)alkyl, aryloxy(1-6C)alkyl, (1-6C)alkylsulfinyl(1-6C)alkyl, (1-6C)alkylsulfonyl(1-6C)alkyl, (2-6C)alkanoylamino(1-6C)alkyl, carbamoyl(1-6C)alkyl; R_2, R_4, R_5 and R_6 are each hydrogen; R_3 is unsubstituted phenyl or phenyl bearing 1, 2 or 3 substituents, which may be the same or different, selected from any of the values for a substituent on R_3 when it is aryl as defined above, including for example (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylthio, halogeno, (2-4C)alkanoylamino, phenoxy, cyano, nitro, hydroxy, trifluoromethyl, (2-4C)alkanoyl, carboxy, hydroxymethyl, benzyloxy, (1-4C)alkoxy(1-4C)alkyl, amino and *N*,*N*-(1-4C)dialkylamino. Within these compounds of the invention, a particular group of compounds of interest are those in which R_1 is (1-6C)alkoxy, especially (1-4C)alkoxy such as methoxy.

In another aspect of the invention, there provided a compound of the formula I, or a pharmaceutically acceptable salt thereof, wherein R_1 is (1-6C)alkoxy, hydroxy-(1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy, (1-6C)alkylthio(1-6C)alkoxy, (1-6C)alkylsulfinyl(1-6C)alkoxy, (1-6C)alkylsulfonyl(1-6C)alkoxy, aryl(1-6C)alkoxy, fluoro(1-6C)alkoxy, carbamoyl(1-6C)alkoxy, (2-6C)alkanoylamino(1-6C)alkoxy, (1-6C)alkoxy-(1-6C)alkyl, aryloxy(1-6C)alkyl, (1-6C)alkylsulfinyl(1-6C)alkyl, (1-6C)alkylsulfonyl(1-6C)alkyl, (2-6C)alkanoylamino(1-6C)alkyl, carbamoyl(1-6C)alkyl; R_2, R_4, R_5 and R_6 are each hydrogen; R_3 is unsubstituted phenyl or phenyl bearing 1, 2 or 3 substituents, which may be the same or different, selected from any of the values for a substituent on R_3 when it is aryl as defined above, including for example (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylthio, halogeno, (2-4C)alkanoylamino, *N*-tert-butylcarbamoyloxymethyl, phenoxy, cyano, nitro, hydroxy, trifluoromethyl, (2-4C)alkanoyl, carboxy, carboxy(1-4C)alkyl, hydroxymethyl, benzyloxy, (1-4C)alkoxy(1-4C)alkyl, aryloxy(1-4C)alkyl, aryloxy(1-4C)alkylcarbamoyl, aryloxy(1-4C)alkylsulfamoyl, amino, *N*,*N*-(1-4C)dialkylamino, *N*-pyrrolidinylcarbonyl and *N*-piperidinylcarbonyl. Within these compounds of the invention, a particular group of

compounds of interest are those in which R_1 is (1-6C)alkoxy, especially (1-4C)alkoxy such as methoxy.

In another aspect of the invention, there is provided a compound of the formula I, or a pharmaceutically acceptable salt thereof, wherein R_1 has any of the values defined above, R_2, R_5 and R_6 are each hydrogen, R_4 is unsubstituted aryl or aryl bearing 1,2 or 3 substituents having any of the values defined above; and R_3 is H, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylthio or halogeno.

In another aspect of the invention, there provided a compound of the formula I, or a pharmaceutically acceptable salt thereof, wherein R_1 is (1-6C)alkoxy, hydroxy-(1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy, (1-6C)alkylthio(1-6C)alkoxy, (1-6C)alkylsulfinyl(1-6C)alkoxy, (1-6C)alkylsulfonyl(1-6C)alkoxy, aryl(1-6C)alkoxy, fluoro(1-6C)alkoxy, carbamoyl(1-6C)alkoxy, (1-6C)alkylcarbonylamino(1-6C)alkoxy, (1-6C)alkoxy-(1-6C)alkyl, aryloxy(1-6C)alkyl, (1-6C)alkylsulfinyl(1-6C)alkyl, (1-6C)alkylsulfonyl(1-6C)alkyl, (2-6C)alkanoylamino(1-6C)alkyl, carbamoyl(1-6C)alkyl; R_2, R_3, R_5 and R_6 are each hydrogen; R_4 is unsubstituted phenyl or phenyl bearing 1, 2 or 3 substituents, which may be the same or different, selected from any of the values for a substituent on R_4 when it is aryl as defined above, including for example (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylthio, halogeno, (2-4C)alkanoylamino, phenoxy, cyano, nitro, hydroxy, trifluoromethyl, (2-4C)alkanoyl, carboxy, hydroxymethyl, benzyloxy, (1-4C)alkoxy(1-4C)alkyl, amino and *N*,*N*-(1-4C)dialkylamino. Within these compounds of the invention, a particular group of compounds of interest are those in which R_1 is (1-6C)alkoxy, especially (1-4C)alkoxy such as methoxy.

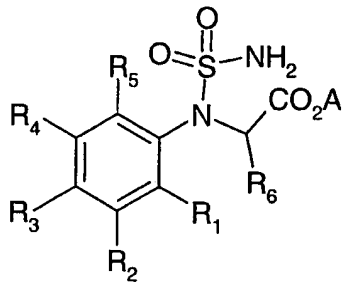
In another aspect of the invention, there provided a compound of the formula I, or a pharmaceutically acceptable salt thereof, wherein R_1 is (1-6C)alkoxy, hydroxy-(1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy, (1-6C)alkylthio(1-6C)alkoxy, (1-6C)alkylsulfinyl(1-6C)alkoxy, (1-6C)alkylsulfonyl(1-6C)alkoxy, aryl(1-6C)alkoxy, fluoro(1-6C)alkoxy, carbamoyl(1-6C)alkoxy, (1-6C)alkylcarbonylamino(1-6C)alkoxy, (1-6C)alkoxy-(1-6C)alkyl, aryloxy(1-6C)alkyl, (1-6C)alkylsulfinyl(1-6C)alkyl, (1-6C)alkylsulfonyl(1-6C)alkyl, (2-6C)alkanoylamino(1-6C)alkyl, carbamoyl(1-6C)alkyl; R_2, R_3, R_5 and R_6 are each hydrogen; R_4 is unsubstituted phenyl or phenyl bearing 1, 2 or 3 substituents, which may be the same or different, selected from any of the values for a substituent on R_4 when it is aryl as defined above, including for example (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylthio, halogeno, (2-4C)alkanoylamino, *N*-tert-butylcarbamoyloxymethyl, phenoxy, cyano, nitro, hydroxy, trifluoromethyl, (2-4C)alkanoyl, carboxy, carboxy(1-4C)alkyl, hydroxymethyl, benzyloxy, (1-

4C)alkoxy(1-4C)alkyl, aryloxy(1-4C)alkyl, aryloxy(1-4C)alkylcarbamoyl, aryloxy(1-4C)alkylsulfamoyl, amino, *N*,*N*-(1-4C)dialkylamino, *N*-pyrrolidinylcarbonyl and *N*-piperidinylcarbonyl. Within these compounds of the invention, a particular group of compounds of interest are those in which R_1 is (1-6C)alkoxy, especially (1-4C)alkoxy such as methoxy.

In another aspect of the invention, compounds of the invention are any one of the Examples, or a pharmaceutically acceptable salt thereof.

Another aspect of the present invention provides a process for preparing a compound of formula (I) or a pharmaceutically acceptable salt thereof which process (wherein variable groups are, unless otherwise specified, as defined in formula (I)) comprises of:

(a) cyclisation of a compound of the formula (II)

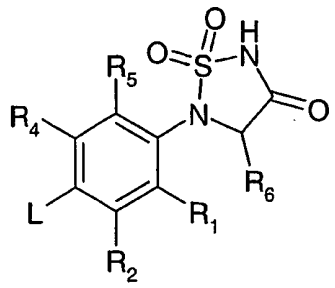


(II)

wherein A is a (1-6C)alkyl, aryl or aryl(1-6C)alkyl group, such as methyl, ethyl or benzyl, or A is a linking group to a solid phase resin, for example polystyrene/Wang resin;

(b) for compounds wherein R_3 is an optionally substituted aryl, optionally substituted biaryl, or optionally substituted heteroaryl group,

reacting a compound of formula (III):

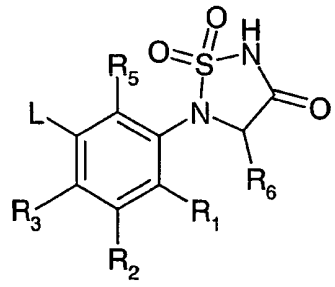


(III)

wherein L is a displaceable group, with a boronic acid of formula R_3-$B(OH)_2$, or ester thereof, or with a compound of the formula R_3-$Sn(Q_1)(Q_2)(Q_3)$ wherein Q_1, Q_2 and Q_3 are independently selected from (1-6C)alkyl and phenyl, the latter optionally substituted by a (1-4C)alkyl, (1-4C)alkoxy or halogeno group, in the presence of a suitable catalyst;

(c) for compounds wherein R_4 is an optionally substituted aryl, optionally substituted biaryl, or optionally substituted heteroaryl group,

reacting a compound of formula (IV):



(IV)

wherein L is a displaceable group, with a boronic acid of formula R_4-$B(OH)_2$, or ester thereof, or with a compound of the formula R_4-$Sn(Q_1)(Q_2)(Q_3)$ wherein Q_1, Q_2 and Q_3 have the meanings defined in (b) above, in the presence of a suitable catalyst;

and thereafter if necessary or desirable:

i) converting a compound of the formula (I) into another compound of the formula (I);

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt thereof.

Suitable values for L include bromo, chloro, iodo, or trifluoromethanesulfonyloxy, particularly bromo. Suitable values for Q_1, Q_2 and Q_3 include, for example, (1-4C)alkyl, such

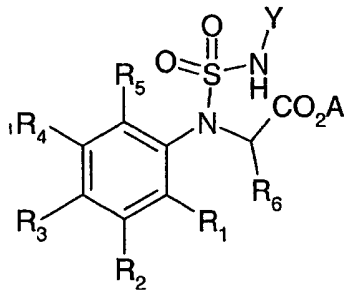
as methyl, ethyl, propyl and butyl. Particularly suitable values for -$Sn(Q_1)(Q_2)(Q_3)$ include -$Sn(methyl)_3$ and -$Sn(butyl)_3$. Suitable catalysts for the reaction are described in the review by N. Miyaura and A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457-2483, and include, for example, palladium(0), palladium(II), nickel(0) and nickel(II) wherein the metal atom is attached to 4 groups independently selected from triphenylphosphine, triphenylphosphite, halogeno and acetyloxy; or palladium(II)halides or nickel(II)halides. Particular catalysts include, for example, tetrakis-(triphenylphosphine)nickel(0), bis(triphenylphosphine)nickel(II) chloride, nickel(II)chloride, palladium(II) chloride, bis(triphenylphosphine)palladium(II) chloride and terakis(triphenylphosphine)palladium(0). The latter catalyst is particularly useful.

The cyclisation of process (a) may be carried out using a base, such as sodium hydride or piperidine. The reaction is generally carried out in an inert solvent or diluent, such as tetrahydrofuran, at or about ambient temperature.

When a boronic acid is used in process (b) or (c), the reaction is carried out in the presence of a suitable base and in the presence of a suitable solvent or diluent. A suitable base for use in the reaction is, for example, an alkali metal alkoxide such as sodium methoxide, an alkali metal carbonate such as sodium carbonate, potassium carbonate or cesium carbonate, or an organic base such as tri(1-6C)alkylamine, for example, triethylamine. An alkali metal carbonate is particularly suitable. A suitable solvent or diluent includes, for example, a hydrocarbon, such as toluene or xylene, an ether, such as dioxan or tetrahydrofuran, an (1-4C)alcohol such as methanol, ethanol or butanol, water, or mixtures thereof. Particularly suitable mixtures of solvents or diluents include, for example, a mixture of dimethoxymethane, ethanol and water and a mixture of toluene, ethanol and water. The reaction is generally performed at a temperature in the range, for example, 50-180°C. Heating with a source of microwave energy is advantageous for these couplings. Compounds of the formula R_3-$B(OH)_2$ and R_4-$B(OH)_2$, or esters thereof, may be obtained by procedures well known in the art, for example by lithiation of a compound R_3-Br or R_4-Br with n-BuLi in THF at -70°C under argon, followed by reaction with a trialkylborate (such as trimethylborate or triisobutylborate) at -70°C. The ester initially formed may be isolated or hydrolysed in situ to the boronic acid by addition, for example by the addition of saturated aqueous ammonium chloride.

When a compound of the formula R_3-Sn(Q_1)(Q_2)(Q_3) and R_4-Sn(Q_1)(Q_2)(Q_3) is used in process (b) or (c), the reaction is generally carried out in the presence of a suitable solvent or diluent, for example a hydrocarbon, such as toluene or xylene, or an ether, such as dioxan or tetrahydrofuran, and at a temperature in the range, for example, 20-150°C. The starting materials may be obtained by procedures well known in the art, or by analogy therewith. For example, compounds of the formula R_3-Br and R_4-Br may be reacted to form a Grignard reagent which is subsequently reacted with a trialkyltin halide, such as tributyltin chloride, in a suitable solvent such as THF, at a temperature in the range of, for example, 0-25°C.

Compounds of the formula (II) may be prepared by deprotection of a compound of the formula (V)

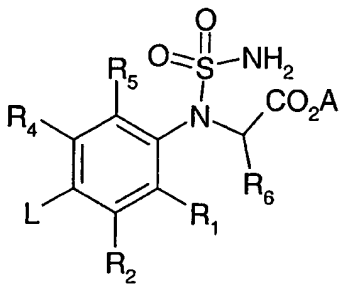


(V)

wherein Y is a protecting group, for example a *tert*-butoxycarbonyl or 9-fluorenylmethoxycarbonyl group.

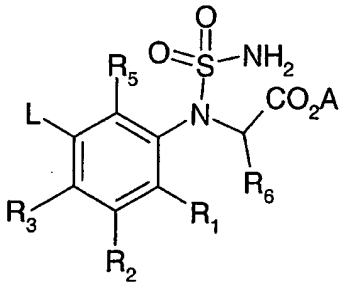
A *tert*-butoxycarbonyl protecting group may be removed under acidic conditions, for example using aqueous trifluoroacetic acid at ambient temperature. A 9-fluorenylmethoxycarbonyl protecting group may be removed using basic conditions, for example using piperidine or 1,8-diazabicyclo[5.4.0]undec-7-ene. When basic conditions are used to remove the protecting group, concomitant cyclisation to a compound of formula (I) may occur.

Compounds of the formula (III) may be prepared by cyclisation of a compound of the formula (VI)



(VI)

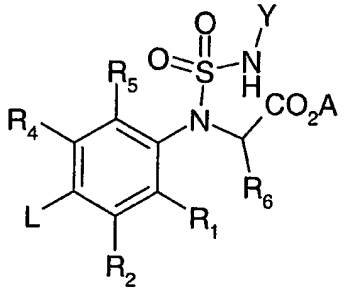
wherein A is a (1-6C)alkyl, aryl or aryl(1-6C)alkyl group, such as methyl, ethyl or benzyl, or A is a linking group to a solid phase resin, for example polystyrene/Wang resin. The cyclisation may be carried out using analogous conditions to those described herein for the cyclisation of a compound of formula (II). Compounds of the formula (IV) may be prepared by cyclisation of a compound of the formula (VII)



(VII)

using an analogous procedure.

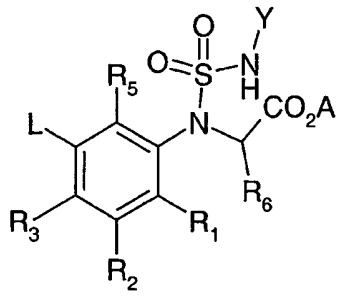
Compounds of the formula (VI) may be prepared by deprotection of a compound of the formula (VIII)



(VIII)

wherein Y is a protecting group, for example a *tert*-butoxycarbonyl or 9-fluorenylmethoxycarbonyl group. A *tert*-butoxycarbonyl protecting group may be removed under acidic conditions, for example using aqueous trifluoroacetic acid at ambient

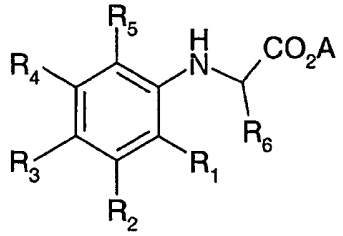
temperature. A 9-fluorenylmethoxycarbonyl protecting group may be removed using basic conditions, for example using piperidine or 1,8-diazabicyclo[5.4.0]undec-7-ene. When basic conditions are used to remove the protecting group, concomitant cyclisation to a compound of formula (III) may occur. Using an analogous procedure a compound of the formula (IX)



(IX)

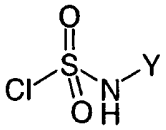
may be deprotected to give a compound of the formula (VII), or (IV) if the deprotection is carried out under basic conditions.

A compound of the formula (V) may be prepared by sulphamoylation of a compound of the formula (X)



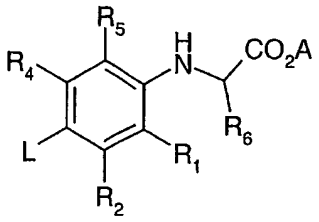
(X)

with a sulphamoylating agent of formula (XI)

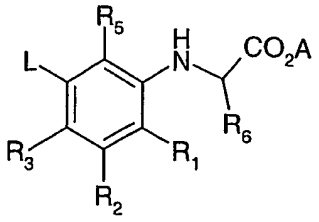


(XI)

wherein Y is a protecting group, for example *tert*-butoxycarbonyl or 9-fluorenylmethoxycarbonyl. Using an analogous procedure, a compound of the formula (VIII) or (IX) may be prepared by sulphamoylation of a compound of the formula (XII) or (XIII) respectively



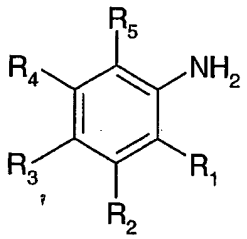
(XII)



(XIII)

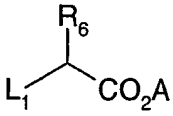
with a sulphamoylating agent of the formula (XI). Compounds of the formula (XI) may be obtained using the methods described by Dewynter in Tetrahedron, 1993, Vol. 49, page 72. The sulphamoylation reaction is generally carried out in the presence of a base, such as triethylamine, in an inert solvent or diluent such as dichloromethane, under an inert atmosphere, such as nitrogen or argon, and at a temperature in the range -10°C to ambient temperature, for example at about 0°C to ambient temperature.

A compound of the formula (X) may be prepared by reaction of a compound of the formula (XIV)



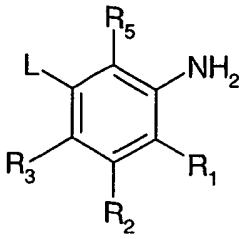
(XIV)

with an alkylating agent of the formula (XV)

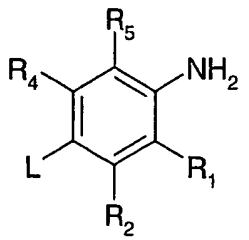


(XV)

wherein L_1 is a displaceable group, for example chloro, bromo, iodo, tosyloxy, mesyloxy or trifluoromethanesulfonyloxy, and A is (1-6C)alkyl, aryl or aryl(1-6C)alkyl, for example methyl, ethyl or benzyl, or A is a linking group to a solid phase resin, for example polystyrene/Wang resin. Using an analogous procedure compounds of the formula (XII) and (XIII) may be obtained by reaction of a compound of the formula (XVI) and (XVII) respectively



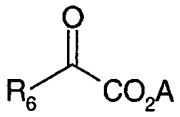
(XVI)



(XVII)

with an alkylating agent of the formula (XV). The alkylation is carried out using procedures well known in the art for alkylation of anilines or as described herein, or by analogy therewith.

Alternatively a compound of the formula (X) may be prepared by reaction of a compound of the formula (XIV) with an aldehyde or ketone of formula (XVIII)



(XVIII)

wherein A and R_6 are as previously defined, in the presence of a reducing agent, for example sodium cyanoborohydride. Using an analogous procedure, compounds of the formula (XII) and (XIII) may be prepared by reaction of a compound of the formula (XVI) and (XVII) respectively with a compound of the formula (XVIII), in the presence of a reducing agent.

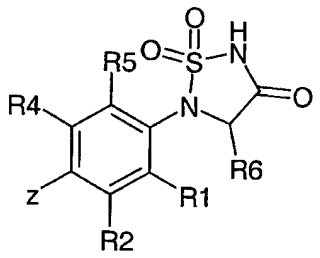
Compounds of the formula (XVI) and (XVII) are commercially available or may be obtained using procedures well known in the art, or by analogy therewith.

As an alternative to method (b) for the preparation of compounds wherein R_3 is an optionally substituted aryl, optionally substituted biaryl, or optionally substituted heteroaryl group, a compound of formula ArL, (wherein L is a displaceable group and Ar represents an optionally substituted aryl, optionally substituted biaryl, or optionally substituted heteroaryl radical) may be reacted with a boronic acid or boronic ester containing compound of formula (XIX) using generic coupling conditions as described previously. Suitable values of L are those described previously. Suitable values for Z are dihydroxyboryl, di(1-6C)alkoxyboryl or cyclic borate esters such as (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl).

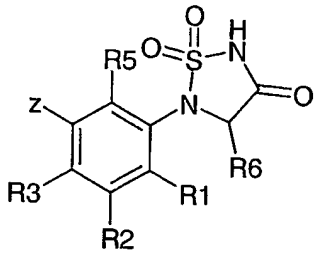
As an alternative to method (c) for the preparation of compounds wherein R_4 is an optionally substituted aryl, optionally substituted biaryl, or optionally substituted heteroaryl group, a compound of formula ArL, (wherein L is a displaceable group and Ar represents a an optionally substituted aryl, optionally substituted biaryl, or optionally substituted heteroaryl

radical) may be reacted with a boronic acid or boronic ester containing compound of formula (XX) using generic coupling conditions as described previously. Suitable values of L are those described previously. Suitable values for Z are dihydroxyboryl, di(1-6C)alkoxyboryl or preferably cyclic borate esters such as (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl).

Compounds of formulae (XIX) and (XX) wherein Z is a cyclic borate ester may be prepared by reaction of a compound where Z is a halogen, preferably iodo, with a borylating agent such as bis(pinacolato)boron in the presence of a suitable catalyst such as [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II).



(XIX)



(XX)

Compounds in which R_3 or R_4 is phenyl substituted with a 3- or 4-(aryloxyalkyl)carbamoyl group may be prepared by coupling of the corresponding 3- or 4-carboxy compounds to the appropriate (aryloxyalkyl)amines, for example by use of the peptide coupling reagents HOBt and EDCI in the presence of a suitable base such as DIPEA. The (aryloxyalkyl)amines may be prepared by coupling appropriately substituted phenolic compounds with appropriately *N*-protected hydroxyalkylamines, for example using triphenylphosphine/DEAD, followed by removing of the protecting group, which is suitably *tert*-butoxycarbonyl.

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the

introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogeno group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or t-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a t-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl

group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a t-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

A further aspect of the invention comprises novel intermediates used in the manufacture of the compounds of formula I.

As stated hereinbefore the compounds defined in the present invention possess PTP1B inhibitory activity. These properties may be assessed using the following assay.

Assay

Expression and purification of human PTP1B

A T7 based expression vector encoding residues 1-321 of human PTP1B was transformed into Escherichia coli K12 host strain DS 410 (DE3). A 600ml seeder of the recombinant was grown in Luria-Bertani medium containing 10μg/ml tetracycline at 37°C for 14 hours to an optical density of 5 at 550nm (which may be expressed as $OD_{550} = 5$) on an orbital shaker with a 2" throw at 250rpm. This was then used to inoculate a 20/l fermenter (Braun U30D). The bacteria were grown at 37°C in high yeast extract (HYE) 20 medium containing 3.0g/l KH_2PO_4, 6.0g/l Na_2HPO_4, 0.5g/l NaCl, 2.0g/l casein hydrolysate, 10.0g/l $(NH_4)_2SO_4$, 35.0g/l glycerol, 20.0g/l yeast extract, 0.5g/l $MgSO_4.7H_2O$, 0.0294g/l $CaCl_2.2H_2O$, 0.008g/l thiamine, 40mg/l $FeSO_4$, 20mg/l citric acid, 10ug/ml tetracycline, and trace elements, pH 6.7. The cells were grown to OD_{550} =14 and induced by addition of isopropyl b-d-thiogalacto-pyranoside (IPTG) to a final concentration of 0.1mM. Cells were harvested after 4 hours induction when the $OD_{550} = 42$ by centrifugation at 3,500g for 30mins and stored at -80°C.

Frozen cell paste is taken, thawed and suspended (10g/ml) in lysis buffer (75mM 2-(*N*-morpholino)ethanesulfonic acid (MES), 1mM EDTA, 1mM DTT, pH6.3). The cells are lysed by two passages through an 'Emulsiflex C5' homogeniser (available from Glen-Creston, 16 Dalston Gardens, Stanmore, HA7 1DA, England) and the soluble fraction clarified by centrifugation (58,000g for 1 hour). The supernatant is passed over an 'SP-Sepharose' column (available from Amersham Biosciences UK Ltd, Amersham Place, Little Chalfont, Bucks, HP7 9NA, England) (typically 0.5ml - 1ml resin per gram of starting paste) pre-equilibrated in lysis buffer. After passaging the supernatant, the column is washed to baseline with 4 column volumes of lysis buffer. Bound proteins are eluted from the column with a 20 column volume 0mM to 500mM sodium chloride gradient. Fractions are collected and those containing PTP1B, as judged by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), are pooled and concentrated using an 'Amicon stirred cell' with a 10,000 molecular weight cut off membrane (available from Millipore (U.K.) Limited, Units 3&5, The Courtyards, Hatters Lane, Watford, WD18 8YH, England). The PTP1B pool is further purified by passing down a 'Superdex 75' (available from Amersham Biosciences UK Ltd) size exclusion column equilibrated in storage buffer(75mM MES, 100mM NaCl, 1mM dithiothreitol (DTT), 1mM ethylenediaminetetraacetic acid (EDTA), 30% glycerol. Fractions are collected and those containing the PTP1B are pooled and stored at –20 ^{o}C prior to use.

Measurement of PTP1B activity

Human PTP1B activity was measured using p-nitrophenol phosphate (pNPP) as a substrate in 384 well microtitre plates. The assay was conducted at room temperature with a final assay volume of 103µl/well.

Compounds were evaluated using a truncated form of PTP1B (corresponding to the first 314 amino acids) as described above. Compounds were prepared in dimethyl sulfoxide (DMSO) and transferred to column 1 of a 96 well microtitre plate. A 1:3 serial dilution of each compound in DMSO was carried out in across the plate.

For enzyme assays, 3µl compound was transferred to each row of a 384 well microtitre assay plate. Each compound was assayed in duplicate at each concentration. 75µl enzyme @ 1.37µg/ml (1.37x final) in assay buffer (50mM (bis[2-hydroxyethyl]imino-tris[hydroxymethyl]methane) pH 7.0, 2mM EDTA, 5mM DTT, 0.001% t-octylphenoxypolyethoxyethanol) was to added to each well and the enzyme and compound

mix, incubated for 10 minutes. The reaction was initiated by the addition of 25µl pNPP at 4.12x final. The compounds were assayed with pNPP either at Km (0.4mM final) or 10x Km (4mM final). Reactions were stopped 15 minutes after the addition of substrate, by the addition of 10µl 1M NaOH.

The enzyme activity was determined by measurement of the absorbance at 405nm. Each plate carried both DMSO vehicle controls (maximum signal) and enzyme buffer controls (minimum signal). Data was calculated with appropriate corrections for absorbance at 405nm of the compounds and pNPP.

Inhibition was expressed as IC_{50} values in µM.

Generally the compounds, when assayed with pNPP at Km (0.4mM final) or 10xKm (4mM final), gave IC_{50} values of 300 µM or less. Example 96 gave an IC_{50} of 4 µM.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

The composition may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository.

In general the above compositions may be prepared in a conventional manner using conventional excipients.

The compound of formula (I), or a pharmaceutically acceptable salt thereof, will normally be administered to a warm-blooded animal at a unit dose within the range 0.1 – 50 mg/kg that normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-1000 mg of active ingredient. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

We have found that the compounds defined in the present invention, or a pharmaceutically acceptable salt thereof, are effective PTB1B inhibitors, and accordingly have value in the treatment of disease states mediated by this enzyme. Such disease states may include, for example, any of those previously referred to herein.

According to a further aspect of the present invention there is provided a compound of

the formula (I) or a pharmaceutically acceptable salt thereof, as defined hereinbefore for use in a method of prophylactic or therapeutic treatment of a warm-blooded animal, such as man, and in particular for use in the treatment of diabetes mellitus.

Thus according to this aspect of the invention there is provided a compound of the formula (I) or a pharmaceutically acceptable salt thereof, as defined hereinbefore for use as a medicament, and more particularly for use as a medicament for producing a PTP1B inhibitory effect in a warm-blooded mammal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the production of a PTP1B inhibitory effect in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of diabetes mellitus.

According to a further feature of this aspect of the invention there is provided a method for producing a PTP1B inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore.

According to a further feature of this aspect of the invention there is provided a method for treating diabetes mellitus in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore.

In addition to their use in therapeutic medicine, the compounds of formula (I), or a pharmaceutically acceptable salt thereof, are also useful as pharmacological tools in the development and standardisation of in vitro and in vivo test systems for the evaluation of the effects of inhibitors of PTP1B in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

The inhibition of PTP1B described herein may be applied as a sole therapy or may involve, in addition to the subject of the present invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. Simultaneous treatment may be in a single tablet or in separate tablets. For example agents

than might be co-administered with PTP1B inhibitors, particularly those of the present invention, may include other antidiabetic agents, such as sulfonylureas and other insulin secretagogues, PPAR γ agonists and other insulin sensitisers, biguanides, glucosidase inhibitors, SGLT2 inhibitors, PPAR α/γ dual agonists, aP2 inhibitors, glycogen phoshporylase inhibitors, glucokinase activators, advanced glycosylation end product inhibitors, meglitinides and insulin.

In the above other pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the invention described herein also apply.

Examples

The invention will now be illustrated in the following non limiting Examples, in which standard techniques known to the skilled chemist and techniques analogous to those described in these Examples may be used where appropriate, and in which, unless otherwise stated:

(i) temperatures are given in degrees Celsius (°C); operations were carried out under an atmosphere of an inert gas such as argon or nitrogen;

(ii) organic solutions were dried over anhydrous sodium sulfate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30 mmHg) with a bath temperature of up to 40°C;

(iii) Examples 1 to 13 and 20 to 76 were conveniently carried out with microwave heating using an 'Emrys' synthesizer (from Personal Chemistry Inc., 2 Hampshire Street, Suite 100, Foxboro, MX, 02035, USA); Examples 14 to 16 were conveniently carried out using a 'Trident' automated library synthesizer (from Argonaut Technologies, 1101 Chess drive, Foster City, CA 94404, USA) under an inert atmosphere;

(iv) Reverse phase HPLC (Prep LC) purification was carried out on a Waters ZQ Fractionlynx system where a Phenomenex column was used (Synergi Polar-RP, 4μ, 80Å, size 100 x 21.20mm) or YMC-ODSAQ, 5μ, size 100 x 20 mm; thin layer chromatography (TLC) was carried out on silica gel plates;

(v) in general, the course of reactions was followed by TLC and LC-MS and reaction times are given for illustration only;

(vi) yields are given for illustration only and are not necessarily those which can be obtained

by diligent process development;

(vii) where given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm), determined at 300 MHz using perdeuterio dimethyl sulphoxide (DMSO-d_6) as solvent;

(viii) chemical symbols have their usual meanings; SI units and symbols are used;

(ix) reduced pressures are given as absolute pressures in Pascals (Pa); elevated pressures are given as gauge pressures in bars;

(x) solvent ratios are given in volume : volume (v/v) terms;

(xi) mass spectra (MS) were run with LC-MS negative ion APCI mass spectrometry; values for m/z are given; generally, only ions which indicate the parent mass are reported and unless otherwise stated the value quoted is (M-H);

(xii) The following abbreviations are used:

Et_2O	diethyl ether
DMF	dimethylformamide;
DCM	dichloromethane
DME	dimethoxyethane;
MeOH	methanol
EtOH	ethanol;
H_2O	water;
TFA	trifluoroacetic acid
THF	tetrahydrofuran
DMSO	dimethylsulfoxide
HOBt	1-hydroxybenzotriazole
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodi-imide hydrochloride
DIPEA	diisopropylethylamine
DEAD	diethylazodicarboxylate

Example 1

5-(4'-Methyl-1,1'-biphenyl-4-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide

Tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$), 17.3-20 mg, ~0.017 mmol, 5mol%) was added as a solid to a 4 ml reaction vial, followed by automated delivery of 7:3:2 DME/EtOH/H_2O (1150 μl), 1.0 M 4-tolylboronic acid in anhydrous DMF (420 μl, 0.42

mmol, 1.2 eq), 0.5 M 5-(4-bromophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide in anhydrous DMF (Method 7; 700 μl, 0.35 mmol, 1.0 eq) and 2.0 M aqueous cesium carbonate (degassed, 210 μl, 0.42 mmol, 1.2 eq) . The mixture was stirred and heated for 600 seconds at 170 °C. The mixture was allowed to cool to ambient temperature and a LC-MS spectrum was obtained of the crude reaction mixture to ensure complete conversion of brominated starting material to biaryl product. The crude organic mixture was submitted for Prep LC and purified to afford the title compound as an off white solid (6 mg). ^{1}H NMR (DMSO-d_6): 7.62 (2H, d), 7.55 (2H, d), 7.26 (2H, d), 7.25 (2H, d), 4.26 (2H, s), 2.35 (3H, s); m/z $(M-H)^-$ 301.

Examples 2 - 6

Using an analogous procedure to that described in Example 1, but starting with 5-(4-bromophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (Method 7) and the appropriate boronic acid, the following compounds were prepared:-

Ex	Compound	^{1}H NMR (DMSO-d_6)	m/z $(M-H)^-$
2[1]	5-(3'-nitro-1,1'-biphenyl-4-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	8.43 (1H, t), 8.14-8.18 (2H, m), 7.9 (2H, d), 7.75 (1H, t), 7.25 (2H, d), 4.22 (2H, s)	332
3[1,2]	5-(3',5'-dichloro-1,1'-biphenyl-4-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.73-7.75 (4H, m), 7.53 (1H, t), 7.19 (2H, d), 4.16 (2H, s)	355
4[1]	5-(3'-methyl-1,1'-biphenyl-4-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.615 (2H, d), 7.46 (1H, s), 7.42 (1H, d), 7.33 (1H, t), 7.19 (2H, d), 7.135 (1H, d), 4.15 (2H, s), 2.39 (3H, s)	301
5[1]	5-(2'-methyl-1,1'-biphenyl-4-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.29-7.32 (3H, m), 7.24-7.27 (2H, m), 7.19-7.21 (3H, m), 4.27 (2H, s), 2.26 (3H, s)	301
6	5-(3'-acetamido-1,1'-biphenyl-4-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	10.02 (1H, s), 7.80 (1H, s), 7.56-7.61 (3H, m), 7.36 (1H, t), 7.305 (1H, d), 7.205 (2H, d), 4.16 (2H, s), 2.08 (3H, s)	344

[1] For incomplete conversions, an additional 5 mol % $Pd(PPh_3)_4$ was added and the reaction mixture was heated for a further 600 seconds at 170 °C

[2] The boronic acid was added as a 0.5 M solution in anhydrous DMF

Example 7

5-(3'-Chloro-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide

Tetrakis(triphenylphosphine)palladium(0) (17.3-20 mg, ~0.017 mmol, 5mol%) was added as a solid to a 4 ml reaction vial, followed by automated delivery of 7:3:2 DME/EtOH/H_2O (1500 µl), 1.0 M 3-chlorophenylboronic acid in anhydrous DMF (420 µl, 0.42 mmol, 1.2 eq), 1.0 M 5-(3-bromophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide in anhydrous DMF (Method 8; 350 µl, 0.35 mmol, 1.0 eq) and 2.0 M aqueous cesium carbonate (degassed, 210 µl, 0.42 mmol, 1.2 eq) . The mixture was stirred and heated for 600 seconds at 170 °C. The mixture was allowed to cool to ambient temperature and the LC-MS spectrum of the crude reaction mixture indicated incomplete conversion of brominated starting material to biaryl product. Additional tetrakis(triphenylphosphine)palladium(0) catalyst (17.3-20 mg, ~0.017 mmol, 5mol%) was added and the mixture heated for 600 seconds at 170 °C. The crude organic mixture was submitted for Prep LC and purified to afford the title compound as an off white solid (16.5 mg). ^{1}H NMR (DMSO-d_6): 7.74 (1H, t), 7.65 (1H, dd), 7.53 (1H, t), 7.43-7.47 (2H, m), 7.34 (1H, t), 7.32 (1H, d), 7.24 (1H, dd), 4.39 (2H, s); m/z $(M-H)^-$ 321.

Examples 8 - 12

Using an analogous procedure to that described in Example 7, but starting with 5-(3-bromophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (Method 8) and the appropriate boronic acid, the following compounds were prepared:-

Ex	Compound	^{1}H NMR (DMSO-d_6)	m/z $(M-H)^-$
8	5-(3'-methyl-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.34-7.48 (5H, m), 7.265 (1H, d), 7.21 (1H, d), 7.16 (1H, dd), 4.34 (2H, s), 2.40 (3H, s)	301
9	5-(4'-methylthio-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.61-7.63 (2H, d), 7.37-7.42 (3H, m), 7.34 (1H, t), 7.265 (1H, d), 7.15 (1H, dd), 4.33 (2H, s), 2.53 (3H, s)	333

10[1]	5-(4'-methyl-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.565 (2H, d), 7.41 (1H, t), 7.36 (1H, t), 7.27-7.31 (3H, m), 7.15 (1H, dd), 4.41 (2H, s), 2.37 (3H, s)	301
11	5-(2'-methyl-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.41 (1H, t), 7.28-7.32 (3H, m), 7.22-7.23 (1H, m), 7.12-7.13 (2H, m), 6.985 (1H, d), 4.39 (2H, s), 2.26 (3H, s)	301
12	5-(3'-acetamido-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	10.08 (1H, s), 7.79 (1H, d), 7.685 (1H, d), 7.39-7.45 (2H, m), 7.36 (1H, t), 7.31 (1H, d), 7.22 (1H, d), 7.14 (1H, dd), 4.34 (2H, s), 2.08 (3H, s)	344

Example 13

5-[3-(1-Benzofuran-2-yl)phenyl]-1,2,5-thiadiazolidin-3-one 1,1-dioxide

5-(3-Bromophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (Method 8, 124 mg, 0.43mmol), 2-benzofuranboronic acid (75mg, 0.46mmol), tetrakis(triphenylphosphine)palladium(0) (56mg, 0.048mmol) and potassium carbonate (267mg, 1.93mmol) in the mixture of ethylene glycol dimethyl ether (7ml) and water (3ml) were heated at 90°C under a nitrogen atmosphere for 16hr. The mixture was acidified with 2M HCl. The aqueous fraction was extracted with dichloromethane. The organic fraction was concentrated and was purified by flash chromatography on silica gel eluted with 10 % MeOH in DCM and further reverse phase HPLC on a YMCAQ C_{18} column using a gradient of acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluant. Evaporation of solvent gave white solid (1.6 mg); m/z 327 ($M\text{-}H^+$); ^1H NMR (CD_3OD): 7.7 (1H, br), 7.6 (2H, t), 7.5 (1H, d), 7.4(1H, t), 7.3(1H, m), 7.2(3H, m), 4,4 (2H, s).

Example 14

5-(4-Methoxy-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide

A solution of 2-methoxy-5-phenylaniline in DMF (3.0 ml, 0.72 M) was added to an aliquot of Polystyrene/Wang/Bromoacetate resin (Method 10; 300 mg, 0.9 meq/g) in a 4 ml reaction vial. The suspension was heated at 50 °C for 5 hours, allowed to cool to ambient temperature, drained, and washed serially with DMF (5 x 2 ml), tetrahydrofuran (5 x 2ml), and dichloromethane (5 x 2ml). A solution of diisopropylethylamine in dichloromethane (0.5 ml,

2M) was added. The reaction vial was cooled to –20 °C and a freshly prepared solution of 9*H*-fluoren-9-ylmethyl chlorosulfonylcarbamate in dichloromethane (2.9 ml, 0.15 M, 0.44meq) was added. The reaction vial was shaken for 2 hours at –20 °C and gradually (over 1 hour) warmed to 0 °C, followed by shaking at ambient temperature for 3 hours. The reaction vial was drained and washed serially with dichloromethane (3 x 2ml), tetrahydrofuran (3 x 2 ml), and DMF (3 x 2ml). An 8% solution of 1,8 diazabicyclo [5.4.0] undec-7-ene in DMF (3 ml) was added to the reaction vial. The reaction vial was shaken for 75 hours at ambient temperature and the liquid contents collected. The remaining resin was washed with DMF (3 x 3 ml) and the washings combined with the initial collected liquid. The solvent was removed at reduced pressure to give the crude product. The crude product was treated with 2ml of methanol and 0.3 meq of formic acid and subjected to reverse phase liquid chromatography. Like fractions were combined, concentrated by rotary evaporation, and dried at 50 °C, under vacuum, overnight to give the title compound (61.7 mg);

^{1}H NMR (DMSO-d_6): 10.11 (brs, 1H), 7.62 (d, 1H), 7.58 (dd, 1H), 7.52 (d, 2H), 7.36 (m, 2H), 7.24 (t, 1H), 7.15 (d, 1H), 4.49 (s, 2H), 3.76 (s, 3H); ^{13}C NMR (DMSO-d_6) 169.4, 155.6, 138.8, 132.92, 129.0, 127.6, 127.5, 127.2, 126.3, 113.6, 56.1, 55.0; m/z $(M-H)^-$ 317.

Examples 15 - 17

The following compounds were made by an analogous process to that described in Example 14, using the appropriate aniline.

Ex	Compound	^{1}H NMR (DMSO-d_6)	m/z $(M-H)^-$
15	5-[3-(1,3-oxazol-5-yl)phenyl]-1,2,5-thiadiazolidin-3-one 1,1-dioxide [starting from 3-(1,3-oxazol-5-yl)aniline]	8.48 (s, 1H), 7.72 (s, 1H), 7.47-7.38 (m, 2H), 7.39 (d, 1H), 7.17 (m, 1H), 4.40 (s, 2H).	278
16	5-(4-cyclohexylphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide [starting from 4-cyclohexylaniline]	7.16 (d, 2H), 7.05 (d, 2H), 4.26 (d, 2H), 2.40-2.44 (m, 1H), 1.55-1.76 (m, 4H), 1.14-1.38 (m, 6H)	293

17	5-(3-benzoylphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide [starting from 3-benzoylaniline]	7.75 (d, 2H), 7.68 (t, 1H), 7.55 (t, 2H), 7.50-7.47 (m, 2H), 7.34 (d, 1H), 7.26 (d, 1H), 4.23 (s, 2H)	315

Example 18

5-(1,1'-Biphenyl-4-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide

5-(4-Bromophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (Method 7, 100 mg, 0.34 mmol) was dissolved in a mixture of THF (5 ml) and 2M aqueous sodium carbonate solution (0.54 ml) containing phenylboronic acid (48.3 mg, 0.39 mmol). The solution was degassed with argon for 15 min then tetrakis(triphenylphosphine)palladium (20 mg, 0.017 mmol) was added and the mixture heated at 100 °C under reflux overnight. Water (10 ml) was added and the mixture extracted with ethyl acetate (10 ml). The aqueous phase was acidified with 2M hydrochloric acid and the precipitate isolated by filtration. This solid was taken up in ethyl acetate and the solution dried ($MgSO_4$), filtered and evaporated under reduced pressure to give 5-(1,1'-biphenyl-4-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (61 mg) as a pale yellow solid; ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): 4.4 (2H, s), 7.2 (2H, d), 7.3 (1H, t), 7.4 (2H, t), 7.6 (4H, m) : m/z 288 (M+)

Example 19

5-(1,1'-Biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide

Using an analogous procedure to that described in Example 18, but starting from 5-(3-bromophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (Method 8), there was obtained 5-(1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide as a pale yellow solid in 55% yield for the final step; ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): 4.5 (2H,s), 7.15 (1H,dd), 7.25 (1H,d), 7.3-7.5 (5H,m), 7.6 (2H,d) : m/z 287 (M-H)

Example 20

5-(4'-Fluoro-4-methoxy-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide

5-(5-Bromo-2-methoxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (49.0 mg, 0.153 mmol, 1.0 eq.), 4-fluorophenylboronic acid (23.5 mg, 0.168 mmol, 1.1 eq.), and cesium carbonate (199.4 mg, 0.612 mmol, 4.0 eq.) were added to a 5 ml reaction vial, followed by addition of 7:3 DME/H_2O (degassed, 4.5 ml), then tetrakis(triphenylphosphine)palladium (0)

($Pd(PPh_3)_4$), 8.5~9.5 mg, ~0.008 mmol, 5mol%) under nitrogen. The mixture was stirred and heated for 1800 seconds at 100°C. The mixture was allowed to cool to ambient temperature and a LC-MS spectrum was obtained of the crude reaction mixture to ensure complete conversion of brominated starting material to biaryl product. Upon complete conversion, the solvent was removed under reduced pressure. The residue was dissolved in water, then acidified with 1M HCl to pH 1~2. The aqueous layer were extracted with ethyl acetate three times. The combined organic layer was evaporated, filtered, then submitted for Prep LC and purified to afford the title compound as an off white solid (27.4 mg). ^{1}H NMR (CD_3OD): 7.69 (d, 1H), 7.58 (m, 3H), 7.16 (m, 3H), 4.53 (s, 2H), 3.93 (s, 3H); m/z $(M-H)^-$ 335.

Examples 21 to 38

Using an analogous procedure to that described in Example 20, but starting with 5-(5-bromo-2-methoxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (Method 14) and the appropriate boronic acid, the following compounds were prepared in yields of between 23 and 75%:-

Ex	Compound	^{1}H NMR (CD_3OD, 400 MHz)	m/z $(M-H)^-$
21	5-(4'-methoxy-4-methoxy-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.66(d, 1H), 7.60(d, 1H), 7.51(d, 2H), 7.20 (d, 1H), 6.98 (d, 2H), 4.93 (s. 1H), 4.53 (s, 2H), 3.93 (s, 3H), 3.83 (s, 3H)	346
22	5-(4'-phenoxy-4-methoxy-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.70 (d, 1H), 7.64 (dd, 2H), 7.59 (dd, 2H), 7.36 (t, 2H), 7.19 (d, 1H), 7.12 (t, 1H), 7.05 (t, 4H), 6.83 (m, 1H), 4.53 (s, 2H), 3.93 (s, 3H)	409
23	5-(3'-cyano-4-methoxy-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.95 (s, 1H), 7.89 (d, 1H), 7.76 (d, 1H), 7.69 (t, 2H), 7.60 (t, 1H), 7.26 (d, 1H), 4.55 (s, 2H), 3.94 (s, 3H)	342
24	5-(3'-nitro-4-methoxy-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	8.46 (s, 1H), 8.20 (d, 1H), 8.04 (d, 1H), 7.84 (d, 1H), 7.77 (d, 1H), 7.70 (t, 1H), 7.29 (d, 1H) 4.56 (s, 2H), 3.97 (s, 3H)	362

25	5-(3'-methoxy-4-methoxy-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.69 (d, 1H), 7.61 (dd, 1H), 7.31 (t, 1H), 7.18 (q, 2H), 7.09 (t, 1H), 6.88 (dd, 1H0, 4.51 (s, 2H), 3.90 (s, 3H), 3.82 (s, 3H)	347
26	5-(3'-hydroxy-4-methoxy-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.67 (d, 1H), 7.61 (dd, 1H), 7.23 (t, 1H), 7.16 (d, 1H), 7.04 (d, 1H), 6.99 (d, 1H), 6.76 (dd, 1H), 4.54 (s, 2H), 3.91 (s, 3H)	333
27	5-(3', 4'-dimethoxy-4-methoxy-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.67 (d, 1H), 7.61 (dd, 1H), 7.15 (m, 3H), 7.02 (d, 1H), 4.52 (s, 2H), 3.92 (s, 3H), 3.90 (s, 3H), 3.86 (s, 3H).	377
28	5-(4'-trifluoromethyl-4-methoxy-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.75 (d, 1H), 7.69 (dd, 3H), 7.60 (t, 1H), 7.50 (dd, 1H), 7.18 (d, 1H), 4.49 (s, 2H0, 3.88 (s, 3H)	385
29	5-(3', 4'-methylenedioxy-4-methoxy-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.62 (d, 1H), 7.55 (dd, 1H), 7.15 (d, 1H), 7.06 (d, 2H), 6.88 (d, 1H), 5.97 (s, 2H), 4.52 (s, 2H), 3.91 (s, 3H).	361
30	5-(3'-acetamido-4-methoxy-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.73 (d, 2H), 7.59 (d, 1H), 7.50 (d, 1H), 7.35 (t, 1H), 7.26 (d, 1H), 7.19 (d, 2H), 4.36 (s, 2H), 3.85 (s, 3H), 2.06 (s, 3H) in DMSO – d_6, 400MHz	374
31	5-(3'-methyl-4-methoxy-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.67 (s, 1H), 7.61 (d, 1H), 7.37 (m, 3H), 7.18 (m, 2H), 4.52 (s, 2H), 3.90 (s, 3H), 2.38 (s, 3H).	331
32	5-(3'-acetyl-4-methoxy-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	8.12 (s, 1H), 7.91 (d, 1H), 7.77 (d, 1H), 7.73 (s, 1H), 7.66 (d, 1H), 7. 53(t, 1H), 7.21 (d, 1H), 4.54 (s, 2H), 3.91 (s, 3H), 2.63 (s, 3H).	359

33	5-(4'-carboxy-4-methoxy-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	8.04 (d, 2H), 7.75 (m, 4H), 7.24 (d, 1H), 4.49 (s, 2H), 3.91 (s, 3H), in CD_3CN, 400 MHz.	361
34	5-(2-methoxy-5-*trans*-styrylphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.67 (d, 1H), 7.52 (m, 3H), 7.33 (t, 2H), 7.23 (t, 1H), 7.08 (m, 3H), 4.50 (s, 2H), 3.90 (s, 3H).	343
35	5-(2-methoxy-5-(2-naphthyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	8.02 (s, 1H), 7.84 (m, 4H), 7.72 (m, 2H), 7.46 (m, 2H), 7.21 (d, 1H), 4.53 (s, 2H), 3.91 (s, 3H).	367
36	5-(4'-hydroxymethyl-4-methoxy-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.71 (d, 1H), 7.64 (dd, 1H), 7.55 (d, 2H), 7.43 (d, 2H), 7.18 (d, 1H0, 4.64 (s, 2H), 4.53 (s, 2H), 3.92 (s, 3H	347
37	5-(3'-acetyl-4-methoxy-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	8.12 (s, 1H), 7.91 (d, 1H), 7.77 (d, 1H), 7.73 (s, 1H), 7.66 (d, 1H), 7. 53(t, 1H), 7.21 (d, 1H), 4.54 (s, 2H), 3.91 (s, 3H), 2.63 (s, 3H).	359
38	5-(4-methoxyl-3'-(methoxymethyl-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	8.57 (d, 1H), 8.36 (s, 1H), 8.10 (d, 2H), 8.02 (t, 2H), 7.21 (d, 1H), 5.07 (s, 2H), 4.71 (s, 2H), 3.97 (s, 3H), 3.95 (s, 3H).	361

Example 39

5-(3'-Benzyloxy-4-methoxy-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide

5-(5-Bromo-2-methoxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (Method 14, 46.0 mg, 0.143 mmol, 1.0 eq.), 3-benzyloxyphenylboronic acid (36.0 mg, 0.158 mmol, 1.1 eq.), and cesium carbonate (186.4 mg, 0.572 mmol, 4.0 eq.) were added to a 5 ml reaction vial, followed by 7:3 DME/H_2O (degassed, 4.5 ml), then tetrakis(triphenylphosphine)palladium (0) ($Pd(PPh_3)_4$), 8.5~9.5 mg, ~0.008 mmol, 5mol%)

was added under nitrogen. The mixture was stirred and heated for 2700 seconds at 100°C. The mixture was allowed to cool to ambient temperature and a LC-MS spectrum was obtained of the crude reaction mixture to ensure complete conversion of brominated starting material to biaryl product. Upon complete conversion, the solvent was removed under reduced pressure. The residue was dissolved in water, extracted with ethyl acetate twice to remove triphenylphosphine, then acidified with 1M HCl to pH 1~2. The aqueous layer were extracted with ethyl acetate three times. The combined organic layer was evaporated, filtered, then submitted for Prep LC and purified to afford the title compound as an off white solid (14.3 mg). ^{1}H NMR (CD_3OD): 7.69 (d, 1H), 7.61 (dd, 1H), 7.45 (d, 2H), 7.37 (m, 4H), 7.18 (m, 3H), 6.94 (dd, 1H), 5.13 (s, 2H), 4.51 (s, 2H), 3.91 (s, 3H); m/z $(M-H)^-$ 423.

Examples 40 to 70

Using an analogous procedure to that described in Example 39, but starting with 5-(5-bromo-2-methoxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (Method 14) and the appropriate boronic acid, the following compounds were prepared in yields of between 5 and 45%:-

Ex	Compound	^{1}H NMR (CD_3OD)	m/z $(M-H)^-$
40	5-(4'-benzyloxy-4-methoxy-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.64 (m, 2H), 7.46 (m, 7H), 7.15 (d, 1H), 7.07 (d, 2H), 5.13 (s, 2H), 4.48 (s, 2H), 3.88 (s, 3H), 3.28 (s, 1H), in CD_3CN, 400 MHz.	423
41	5-(2-methoxy-5-*cis*-styrylphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.32 (s, 1H), 7.23 (m, 6H), 6.98 (d, 1H), 6.56 (q, 2H), 4.39 (s, 2H), 3.86 (s, 3H).	343
42	5-(4'-*tert*-butoxymethyl-4-methoxy-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.73 (d, 1H), 7.64 (dd, 1H), 7.55 (d, 2H), 7.41 (d, 2H), 7.21 (d, 1H), 4.51 (d, 4H), 3.93 (3H), 1.32 (s, 9H).	403

43	5-(3'-carboxy-4-methoxy-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	8.22 (s, 1H), 7.97 (d, 1H), 7.80 (d, 1H), 7.75 (d, 1H), 7.68 (dd, 1H), 7.53 (t, 1H), 7.22 (d, 1H), 4.55 (s, 2H0, 3.93 (s, 3H)	361
44	5-(4'-methoxymethyl-4-methoxy-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.72 (d, 1H), 7.64 (dd, 1H), 7.56 (d, 2H), 7.38 (d, 2H), 7.21 (d, 1H), 4.52 (s, 2H), 4.48 (s, 2H), 3.92 (s, 3H), 3.39 (s, 3H).	361
45	5-(3'-methylthio-4-methoxy-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.72 (s, 1H), 7.62 (dd, 1H), 7.45 (s, 1H), 7.34 (d, 2H), 7.21 (m, 2H), 4.52 (s, 2H), 3.93 (s, 3H), 2.52 (s, 3H).	363
46	5-(2'-acetyl-4-methoxy-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.55 (t, 2H), 7.42 (m, 3H), 7.35 (dd, 1H), 7.23 (d, 1H), 4.54 (s, 2H), 3.94 (s, 3H0, 2.13 (s, 3H)	359
47	5-(3'-fluoro-4-methoxy-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.73 (s, 1H), 7.65 (dd, 1H), 7.40 (m, 2H), 7.30 (d, 1H), 7.22 (d, 1H), 7.04 (m, 1H), 4.52 (s, 2H), 3.93 (s, 3H).	335
48	5-(3', 5'-difluoro-4-methoxy-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.75 (d, 1H), 7.66 (dd, 1H), 7.21 (m, 3H), 6.88 (m, 1H), 4.53 (s, 2H), 3.93 (s, 3H).	353
49	5-(2'-methoxy, 5'-fluoro-4-methoxy-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.66 (d, 1H), 7.52 (dd, 1H), 7.17 (d, 1H), 7.04 (m, 3H), 4.49 (s, 2H), 3.93 (s, 3H), 3.79 (s, 3H).	365
50	5-(4-methoxy-*m*-terphenyl-3-yl)- 1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.79 (d, 2H), 7.65 (m, 3H), 7.55 (d, 2H), 7.45 (m, 3H), 7.35 (t, 1H), 7.20 (d, 1H), 4.51 (s, 2H), 3.93 (s, 3H).	393

51	5-(2'-fluoro-4-methoxy-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.65 (s, 1H), 7.59 (dd, 1H), 7.46 (m, 1H), 7.33 (m, 1H0, 7.23 (m, 3H), 4.53 (s, 2H), 3.94 (s, 3H).	335
52	5-(4'-methylthio-4-methoxy-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.67 (dd, 2H), 7.54 (d, 2H), 7.33 (d, 2H), 7.17 (d, 1H), 4.50 (s, 2H), 3.90 (s, 3H), 3.29 (s, 1H), 2.51 (s, 3H), in CD_3CN, 400 MHz.	363
53	5-(4'-butyl-4-methoxy-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.69 (d, 1H), 7.61 (dd, 1H), 7.47 (d, 2H), 7.23 (d, 2H), 7.17 (d, 1H), 4.52 (s, 2H), 3.91 (s, 3H), 2.64 (t, 2H), 1.63 (m, 2H), 1.37 (m, 2H), 0.95 (t, 3H).	373
54	5-(4-methoxy-*p*-terphenyl-3-yl)- 1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.81 (s, 1H), 7.71 (s, 1H), 7.69 (m, 4H), 7.66 (d, 2H), 7.45 (t, 2H), 7.34 (t, 1H), 7.21 (d, 1H), 4.52 (s, 2H), 3.94 (s, 3H)	393
55	5-(3'-chloro- 4'-fluoro-4-methoxy-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.89 (s, 1H), 7.60 (d, 1H), 7.24 (dd, 1H), 7.16 (d, 1H), 6.98 (t, 1H), 6.70 (d, 1H), 4.42 (s, 2H), 3.53 (s, 3H).	368
56	5-(4-methoxy-3'-fluoro-p-terphenyl-3-yl)- 1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.76 (d, 2H), 7.60 (t, 2H), 7.49 (m, 6H), 7.21 (d, 1H), 4.51 (s, 2H), 3.92 (s, 3H), 3.29 (s, 1H), in CD_3CN, 400 MHz.	411
57	5-(3'-trifluoromethyl-4-methoxy-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.90 (s, 1H), 7.87 (d, 1H), 7.75 (m, 2H), 7.64 (m, 2H), 7.21 (d, 1H), 4.51 (s, 2H), 3.91 (s, 3H), 3.29 (s, 1H), in CD_3CN, 400 MHz.	385
58	5-{5-[(E)-2-(4-chlorophenyl)vinyl]-2-methoxyphenyl)}-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.62 (d, 2H), 7.58 (d, 1H), 7.52 (d, 2H), 7.39 (d, 2H), 7.14 (d, 2H), 4.47 (s, 2H), 3.88 (s, 3H), in CD_3CN, 400 MHz.	378

59	5-(4-methoxy-4-vinyl-1,1-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.75 (s, 1H), 7.66 (d, 1H), 7.58 (d, 2H), 7.51 (d, 2H), 7.21(d, 1H), 6.77 (m, 1H), 5.83 (d, 1H), 5.25 (d, 1H), 4.51 (s, 2H), 3.93 (s, 3H)	343
60	5-[5-(2-furyl)-2-methoxyphenyl]-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.82 (s, 1H), 7.73 (d, 1H), 7.54 (s, 1H), 7.18 (d, 1H), 6.69 (s, 1H), 6.47 (s, 1H), 4.50 (s, 2H), 3.91 (s, 3H).	307
61	5-[5-(1-benzothien-2-yl)-2-methoxyphenyl]-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.85 (m, 3H), 7.59 (m, 2H), 7.34 (, 2H), 7.22 (d, 1H), 4.54 (s, 2H), 3.95 (s, 3H)	373
62	5-[5-(1-benzofuran-2-yl)-2-methoxyphenyl]-1,2,5-thiadiazolidin-3-one 1,1-dioxide	8.10 (s, 1H), 7.76 (s, 1H), 7.62 (d, 2H), 7.26 (d, 4H), 4.24 (s, 2H), 3.86 (s, 3H), in DMSO-d6, 400 MHz.	357
63	5-(4'-acetyl-4-methoxy-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	8.02 (d, 2H), 7.89 (s, 1H), 7.77 (d, 2H), 7.68 (d, 1H), 7.23 (d, 1H), 4.33 (s, 2H), 3.86 (s, 3H), 2.60 (s, 3H), in DMSO-d6, 400 MHz.	359
64	5-(3'-carbamoyl-4-methoxy-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	8.02 (d, 2H), 7.78 (m 2H), 7.67 (d, 1H), 7.54 (d, 1H), 7.45 (t, 1H), 7.35 (s, 1H), 7.14 (d, 1H), 4.28 (s, 2H), 3.79 (s, 3H), in DMSO-d6, 400 MHz.	360
65	5-[2-methoxy-5-(*1H*-pyrazol-4-yl)phenyl]-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.97 (s, 2H), 7.64 (s, 1H), 7.53 (d, 1H), 7.11 (d, 1H), 4.40 (s, 2H), 3.81 (s, 3H), in DMSO-d6, 400 MHz.	307
66	5-[4-methoxy-4-(pyrrolidin-1-ylcarbonyl)-1,1'-biphenyl-3-yl]-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.85 (s, 1H), 7.62 (tt, 5H), 7.19 (d, 1H), 4.34 (s, 2H), 3.86 (s, 3H), 3.46 (m, 4H), 1.88 (m, 4H), in DMSO-d6, 400 MHz.	414

67	5-[4'-(2-carboxyethyl)-4-methoxy-1,1'-biphenyl-3-yl]-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.77 (s, 1H), 7.49 (m, 3H), 7.30 (d, 2H), 7.15 (d, 1H), 4.31 (s, 2H), 3.84 (s, 3H), 2.84 (t, 2H), 2.56 (t, 2H), in DMSO-d6, 400 MHz.	389
68	5-[3'-(tert-butoxycarbonylamino)methyl-4-methoxy-1,1'-biphenyl-3-yl]-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.77 (s, 1H), 7.53 (d, 2H), 7.45 (d, 2H), 7.40 (t, 1H), 7.19 (d, 2H), 4.33 (s, 2H), 4.18 (d, 2H), 3.85 (s, 3H), 1.40 (s, 9H), in DMSO-d6, 400 MHz.	446
69	5-[3'-(N,N-dimethylcarbamoyl)-4-methoxy-1,1'-biphenyl-3-yl]-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.83 (s, 1H), 7.68 (m, 2H), 7.60 (s, 1H), 7.51 (t, 1H), 7.35 (d, 1H), 7.23 (d, 1H), 4.48 (s, 2H), 3.86 (s, 3H), 3.00 (s, 3H), 2.93 (s, 3H), in DMSO-d6, 400 MHz.	388
70	5-[4'-(N-cyclohexylcarbamoyl)-4-methoxy-1,1'-biphenyl-3-yl]-1,2,5-thiadiazolidin-3-one 1,1-dioxide	8.22 (d, 1H), 7.91 (d, 2H), 7.85 (s, 1H), 7.66 (m, 3H), 7.21 (d, 1H), 4.40 (s, 2H), 3.86 (s, 3H), 1.84 (d, 4H), 1.64 (d, 1H), 1.32 (m, 4H), 1.15 (m, 2H), in DMSO-d6, 400 MHz.	442

Example 71

5-(3'-Amino-4-methoxy-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide

5-(5-Bromo-2-methoxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (Method 14, 44.4 mg, 0.138 mmol, 1.0 eq.), 3-aminophenylboronic acid (23.6 mg, 0.152 mmol, 1.1 eq.), and cesium carbonate (179.8 mg, 0.552 mmol, 4.0 eq.) were added to a 5 ml reaction vial, followed by 7:3 DME/H_2O (degassed, 4.5 ml), then tetrakis(triphenylphosphine)palladium (0) ($Pd(PPh_3)_4$), 8.0~9.0 mg, ~0.007 mmol, 5mol%) was added under nitrogen. The mixture was stirred and heated for 1,800 seconds at 100 °C. The mixture was allowed to cool to ambient temperature and a LC-MS spectrum was obtained for the crude reaction mixture to ensure complete conversion of brominated starting material to biaryl product. Upon complete conversion, the solvent was removed under reduced pressure. The residue was dissolved in water, extracted twice with ethyl acetate, acidified with 1M HCl to pH 6~7, then water was

removed, filtered, and the crude compound was submitted for preparative LC and purified to afford the title compound as an off white solid, then the product was treated with HCl solution to make a HCl salt. (27.9 mg). ^{1}H NMR (DMSO – d_6): 7.79 (s, 1H), 7.52 (d, 1H), 7.48 (d, 2H), 7.46 (d, 1H), 7.23 (d, 1H), 3.50 (m, 1H), 4.38 (s, 2H), 3.86 (s, 3H); m/z $(M-H)^-$, 332.

Examples 72 to 76

Using an analogous procedure to that described in Example 71, but starting with 5-(5-bromo-2-methoxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (Method 14) and the appropriate boronic acid, the following compounds were prepared in yields of between 35 and 76%:-

Ex	Compound	^{1}H NMR (DMSO-d_6, 400 MHz)	m/z $(M-H)^-$
72	5-(4'-dimethylamino-4-methoxy-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.73 (m, 3H), 7.66 (m, 3H), 7.21 (d, 1H), 4.50 (s, 2H), 3.90 (s, 3H). 3.39 (s, 6H), in CD_3OD	360
73[1]	5-(2-methoxy-5-(4-pyridyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	8.84 (d, 2H), 8.21 (d, 2H), 8.15 (s, 1H), 7.91 (dd, 1H), 7.31 (d, 1H), 4.26 (s, 2H), 3.91 (s, 3H)	318
74	5-(4-hydroxy-4-methoxy-1,1-biphenyl-3-yl)-1,2,5-thiazolidin-3-one 1,1-dioxide	9.45 (s, 1H), 7.68 (s, 1H), 7.46 (d, 1H), 7.39 (d, 2H), 7.14 (d, 1H), 6.82 (d, 2H), 4.36 (s, 2H), 3.82 (s, 3H)	333
75	5-[5-(1*H*-indol-6-yl)-2-methoxyphenyl]-1,2,5-thiadiazolidin-3-one 1,1-dioxide	11.14 (s, 1H), 7.78 (s, 1H), 7.61 (m, 3H), 7.37 (t, 1H), 7.21 (m, 2H), 6.44 (s, 1H), 4.46 (s, 2H), 3.86 (s, 3H)	356
76	5-[2-methoxy-5-(thien-2-yl)phenyl]-1,2,5-thiazolidin-3-one 1,1-dioxide	7.74 (s, 1H), 7.59 (d, 1H), 7.48 (d, 1H), 7.39 (d, 1H), 7.16 (d, 1H), 7.11 (t, 1H), 4.41 (s, 2H), 3.84 (s, 3H).	323

[1]Reaction complete after 5400 seconds at 100°C.

Example 77

5-[2-Methoxy-5-(phenylethynyl)phenyl]-1,2,5-thiadiazolidin-3-one 1,1-dioxide

5-(5-Iodo-2-methoxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (Method 32, 368 mg, 1 mmol), CuI (3.9 mg, 0.02 mmol), $Pd(PhCN)_2Cl_2$ (11.5 mg, 0.03 mmol) and diisopropylamine (166 µL, 1.18 mmol) were dissolved in dry dioxane (3 mL) under an inert atmosphere. Phenyl acetylene was added (131 µL, 1.3 mmol) followed by a solution of tri(*t*-Butyl)phosphine (0.25 M in hexanes, 260 µL, 0.065 mmol). The solution was stirred at room temperature for 16 h under inert atmosphere, diluted with ethyl acetate (5 mL) and filtered through a pad of Celite. The solvent was evaporated and the residue purified by reverse phase HPLC (SB-C18 Zorbax column 9.4 x 150 mm, gradient 5-95% acetonitrile, 0.1 % TFA, flow rate = 7mL/ min, 13.3 min run time, 25°C, scanning 220 to 400nm) to give the title product (82 mg).

^{1}H NMR (DMSO-d_6) 3.84 (s, 3H), 4.32 (s, 2H), 7.14 (d, 1H), 7.39-7.41 (m, 3H), 7.45 (d, 1H), 7.53-7.55 (m, 2H), 7.67 (d, 1H). MS: m/z $(M-H)^-$ 241

The following compounds were made by an analogous process to that described in Example 77, using the appropriate acetylene

Example	Compound	^{1}H NMR (DMSO-d_6)	m/z $(M-H)^-$
78	5-[2-methoxy-5-(3-phenylprop-1-yn-1-yl)phenyl]-1,2,5-thiadiazolidin-3-one 1,1-dioxide [starting from benzylacetylene]	7.54 (d, 1H), 7.32-7.40 (m, 4H), 7.26 (m, 1H), 7.09 (d, 1H), 4.35 (s, 2H), 3.86 (s, 2h), 3.81 (s, 3H)	355
79	5-(5-ethynyl-2-methoxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide [starting from trimethylsilylacetylene]	7.10 (d, 1H), 7.44 (d, 1H), 7.55 (d, 1H), 4.31 (s, 2H), 3.80 (s, 3H), 2.86 (s, 1H)	265

Example 80

This example is Method 9.

Example 81: 5-{3'-[2-(2-carboxy-3-hydroxyphenoxy)ethyl]-4-methoxy-1,1'-biphenyl-3-yl}-1,2,5-thiadiazolidin-3-one 1,1-dioxide and

Example 82: 5-{4-methoxy-3'-[2-(3-hydroxy-2-methoxycarbonylphenoxy)ethyl]-1,1'-biphenyl-3-yl}-1,2,5-thiadiazolidin-3-one 1,1-dioxide

To a degassed solution of methyl 2-[2-(3-bromophenyl)ethoxy]-6-hydroxybenzoate (Method 19, 164 mg, 0.47 mmol), 5-[2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,2,5-thiadiazolidin-3-one 1,1-dioxide (Method 16, 172 mg, 0.47 mmol) and cesium carbonate (609 mg, 1.87 mmol) under an inert atmosphere was added $Pd(PPh_3)_4$ (54 mg, 0.047 mmol) and heated to 85 °C for 2 hours. Upon cooling the mixture was partitioned between EtOAc (50 ml) and 1M HCl aq (30 ml). The EtOAc layer was dried (Na_2SO_4), filtered and evaporated to give a dark brown gum. Purification was by reverse phase preparative chromatography through a Phenomenex LUNA 150 x 21.2 mm 10u C18 column using acetonitrile (B) and 5% (v/v) NH_3 in H_2O (A) as eluent and gradient of 1:20 B:A to 7:13 B:A. The pure product fractions were partitioned between EtOAc (50 ml) and 1M HCl aq (30 ml). The EtOAc layer was dried (Na_2SO_4), filtered and evaporated to give the title compounds as colourless, clear gums. Yields:- 5-{3'-[2-(2-carboxy-3-hydroxyphenoxy)ethyl]-4-methoxy-1,1'-biphenyl-3-yl}-1,2,5-thiadiazolidin-3-one 1,1-dioxide (45mg, 19%) and 5-{4-methoxy-3'-[2-(3-hydroxy-2-methoxycarbonylphenoxy)ethyl]-1,1'-biphenyl-3-yl}-1,2,5-thiadiazolidin-3-one 1,1-dioxide (76mg, 32%).

5-{3'-[2-(2-carboxy-3-hydroxyphenoxy)ethyl]-4-methoxy-1,1'-biphenyl-3-yl}-1,2,5-thiadiazolidin-3-one 1,1-dioxide (CD_3OD) 7.61 (d, 1H), 7.55 (dd, 1H), 7.44 (s, 1H), 7.35 (d, 1H), 7.30-7.23 (m, 2H), 7.18 (d, 1H), 7.09 (d, 1H), 6.50 (d, 1H), 6.47 (d, 1H), 4.42 (s, 2H), 4.34 (t, 2H), 3.82 (s, 3H), 3.10 (t, 2H); m/z $(M-H)^-$ 497

5-{4-methoxy-3'-[2-(3-hydroxy-2-methoxycarbonylphenoxy)ethyl]-1,1'-biphenyl-3-yl}-1,2,5-thiadiazolidin-3-one 1,1-dioxide (CD_3OD) 7.61 (d, 1H), 7.54 (dd, 1H), 7.42 (s, 1H), 7.32 (d, 1H), 7.25 (t, 1H), 7.18-7.06 (m, 3H), 6.39 (d, 1H), 6.36 (d, 1H), 4.42 (s, 2H), 4.13 (t, 2H), 3.81 (s, 3H), 3.62 (s, 3H), 3.01 (t, 2H); m/z $(M-H)^-$ 511

The following examples were prepared from the appropriate intermediate in a similar manner to that described above: -

Ex	Compound	NMR (CH_3OD)	M/z $(M-H)^-$
83	5-{4-methoxy-3'-[(3-hydroxy-2-methoxycarbonylphenoxy)methyl]-1,1'-biphenyl-3-yl}-1,2,5-thiadiazolidin-3-one 1,1-dioxide Starting material: see patent application JP08291110	7.64 (d, 1H), 7.61 (s, 1H), 7.57 (dd, 1H), 7.42 (d, 1H), 7.37-7.28 (m, 2H), 7.17 (t, 1H), 7.11 (d, 1H), 6.52 (d, 1H), 6.42 (d, 1H), 5.07 (s, 2H), 4.43 (s, 2H), 3.83 (s, 3H), 3.77 (s, 3H)	497
84	5-{4'-[(2-carboxy-3-hydroxyphenoxy)methyl]-4-methoxy-1,1'-biphenyl-3-yl}-1,2,5-thiadiazolidin-3-one 1,1-dioxide Starting material – Method 18	7.62 (d, 1H), 7.57 (dd, 1H), 7.51 (d, 2H), 7.46 (d, 2H), 7.27 (t, 1H), 7.11 (d, 1H), 6.58 (d, 1H), 6.50 (d, 1H), 5.17 (s, 2H), 4.43 (s, 2H), 3.83 (s, 3H)	483
85	5-{4-methoxy-4'-[(3-hydroxy-2-methoxycarbonylphenoxy)methyl]-1,1'-biphenyl-3-yl}-1,2,5-thiadiazolidin-3-one 1,1-dioxide Starting material – Method 18	7.72 (d, 1H), 7.67 (dd, 1H), 7.59 (d, 2H), 7.54 (d, 2H), 7.27 (t, 1H), 7.19 (d, 1H), 6.60 (d, 1H), 6.53 (d, 1H), 5.13 (s, 2H), 4.53 (s, 2H), 3.91 (s, 3H), 3.87 (s, 3H)	497
86	5-{4'-[2-(2-carboxy-3-hydroxyphenoxy)ethyl]-4-methoxy-1,1'-biphenyl-3-yl}-1,2,5-thiadiazolidin-3-one 1,1-dioxide Starting material – Method 20	7.59 (d, 1H), 7.51 (dd, 1H), 7.41 (d, 2H), 7.28-7.22 (m, 3H), 7.06 (d, 1H), 6.48 (d, 1H), 6.46 (d, 1H), 4.41 (s, 2H), 4.29 (t, 2H), 3.80 (s, 3H), 3.05 (t, 2H)	497
87	5-{4-methoxy-4'-[2-(3-hydroxy-2-methoxycarbonylphenoxy)ethyl]-1,1'-biphenyl-3-yl}-1,2,5-thiadiazolidin-3-one 1,1-dioxide Starting material – Method 20	7.62 (d, 1H), 7.53 (dd, 1H), 7.42 (d, 2H), 7.27 (d, 2H), 7.14 (t, 1H), 7.09 (d, 1H), 6.41 (d, 1H), 6.38 (d, 1H), 4.41 (s, 2H), 4.13 (t, 2H), 3.82 (s, 3H), 3.73 (s, 3H), 2.99 (t, 2H)	497

88	5-{3'-[3-(2-carboxy-3-hydroxyphenoxy)propyl]-4-methoxy-1,1'-biphenyl-3-yl}-1,2,5-thiadiazolidin-3-one 1,1-dioxide Starting material – Method 21	7.54 (d, 1H), 7.47 (dd, 1H), 7.32-7.19 (m, 4H), 7.08 (d, 1H), 7.05 (d, 1H), 6.45 (d, 1H), 6.41 (d, 1H), 4.41 (s, 2H), 4.03 (t, 2H), 3.81 (s, 3H), 2.79 (t, 2H), 2.07 (m, 2H)	511
89	5-{4-methoxy-3'-[3-(3-hydroxy-2-methoxycarbonylphenoxy)propyl]-1,1'-biphenyl-3-yl}-1,2,5-thiadiazolidin-3-one 1,1-dioxide Starting material – Method 21	7.65 (d, 1H), 7.54 (dd, 1H), 7.45-7.28 (m, 3H), 7.24-7.12 (m, 3H), 6.45 (d, 1H), 6.41 (d, 1H), 4.51 (s, 2H), 3.99 (t, 2H), 3.94 (s, 3H), 3.92 (s, 3H), 2.92 (t, 2H), 2.11 (m, 2H)	525
90	5-{4'-[3-(2-carboxy-3-hydroxyphenoxy)propyl]-4-methoxy-1,1'-biphenyl-3-yl}-1,2,5-thiadiazolidin-3-one 1,1-dioxide Starting material – Method 17	7.58 (d, 1H), 7.51 (dd, 1H), 7.37 (d, 2H), 7.24 (t, 1H), 7.17 (d, 2H), 7.07 (d, 1H), 6.46 (d, 1H), 6.42 (d, 1H), 4.42 (s, 2H), 4.03 (t, 2H), 3.80 (s, 3H), 2.75 (t, 2H), 2.03 (m, 2H)	525
91	5-{4-methoxy-4'-[3-(3-hydroxy-2-methoxycarbonylphenoxy)propyl]-1,1'-biphenyl-3-yl}-1,2,5-thiadiazolidin-3-one 1,1-dioxide Starting material – Method 17	7.68 (d, 1H), 7.63 (dd, 1H), 7.53-7.45 (m, 2H), 7.31-7.15 (m, 4H), 6.48 (d, 1H), 6.44 (d, 1H), 4.54 (s, 2H), 3.97 (t, 2H), 3.94 (s, 3H), 3.92 (s, 3H), 2.85 (t, 2H), 2.11 (m, 2H)	525

Example 92: 5-{4-Methoxy-3'-[(2-carboxy-3-hydroxyphenoxy)methyl]-1,1'-biphenyl-3-yl}-1,2,5-thiadiazolidin-3-one 1,1-dioxide

Methyl 2-hydroxy-6-[(3-iodobenzyl)oxy]benzoate (patent application JP08291110, 114 mg, 0.30 mmol) was dissolved in a mixture of DMSO (1.65 ml), DME (2 ml) and water (3.8 ml) containing cesium carbonate (433 mg 1.33 mmol) and 5-[2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,2,5-thiadiazolidin-3-one 1,1-dioxide (Method 16, 121.4 mg, 0.33 mmol). The solution was degassed with argon for 15 min then

tetrakis(triphenylphosphine)palladium (20 mg, 0.017mmol) was added and the mixture heated at 90 °C under reflux for 8 hours. Water (5 ml) was added and the mixture extracted with ethyl acetate (10 ml). The aqueous phase was acidified with 1 M hydrochloric acid and the mixture extracted with ethyl acetate (3x10 ml), washed with water (3 ml) and brine (3 ml), dried (MgSO4), filtered and evaporated under reduced pressure to give a gum which was triturated with water, filtered and dried under reduced pressure over P_2O_5 to give the title product (120 mg) as a pale tan solid ^{1}H NMR (DMSO-d6, 300 MHz, ppm): 10.3(H,b), 7.74(H,d), 7.68(H,s)7.63(H,dd), 7.53(H,d), 7.42(2H,m), 7.19(2H,dd), 6.6(H,d), 6.5(H,d) 5.2(2H,s), 4.5(2H,s), 3.85(3H,s), : m/Z 483 (M-H)

Example 93: 5-{4-Methoxy-3'-[*N*-(2-phenoxyethyl)carbamoyl]-1,1'-biphenyl-3-yl}-1,2,5-thiadiazolidin-3-one 1,1-dioxide

To a stirred solution of 5-(3'-carboxy-4-methoxy-1,1'-biphen-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (Example 43) (0.05 g, 0.14 mmol, 1 eq.) and DIPEA (24 µL, 0.14 mmol, 1 eq.) in DCM (2mL) added HOBt (19 mg, 0.14 mmol, 1 eq.), 2-phenoxyethylamine (18 µL, 0.14 mmol, 1 eq.) and EDCI (31 mg, 0.17 mmol, 1.2 eq.). The reaction was allowed to stir at ambient temperature overnight and then the solvent was removed under reduced pressure. The residue was taken up in acetonitrile:water (1:1, 3 mL) and purified by reverse phase preparative HPLC to afford the title compound as a colourless solid (0.04 g, 60% yield). ^{1}H NMR (CD_3OD): 8.05 (s, 1H), 7.75 (m, 4H), 7.52 (t, 1H), 7.24 (m, 3H), 6.93 (m, 3H), 4.54 (s, 2H), 4.19 (t, 2H), 3.95 (s, 3H), 3.79 (t, 2H); m/z $(M-H)^-$ 480.

Examples 94 to 97

Using an analogous procedure to that described in Example 93, starting with 5-(3'-carboxy-4-methoxy-1,1'-biphen-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (Example 43) and the appropriate amine (Methods 26 to 29) the following compounds were prepared in yields of 19-47%:-

Ex	Compound	^{1}H NMR (DMSO-d_6)	m/z $(M-H)^-$
94	5-(4-methoxy-3'-{*N*-[2-(3-hydroxy-2-methoxycarbonylphenoxy)ethyl] carbamoyl}-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	9.91 (br. s, 1H), 8.68 (t, 1H), 8.08 (s, 1H), 7.78 (m, 3H), 7.70 (m, 1H), 7.55 (t, 1H), 7.25 (d, 1H), 7.18 (t, 1H), 6.58 (d, 1H), 6.50 (d, 1H), 4.45 (s, 2H), 4.10 (t, 2H), 3.85 (s, 3H), 3.65 (s, 3H) 3.50 (m, 2H)	554
95	5-(4-methoxy-3'-{*N*-[3-(3-hydroxy-2-methoxycarbonylphenoxy) propyl]carbamoyl}-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	9.94 (br. s, 1H), 8.63 (t, 1H), 8.06 (s, 1H), 7.75 (m, 4H), 7.54 (t, 1H), 7.23 (d, 1H), 7.19 (t, 1H), 6.50 (m, 2H), 4.42 (s, 2H), 4.05 (t, 2H), 3.85 (s, 3H), 3.77 (s, 3H), 3.40 (m, 2H), 1.95 (m, 2H)	568
96	5-(4-methoxy-3'-{*N*-[5-(3-hydroxy-2-methoxycarbonylphenoxy) pentyl]carbamoyl}-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	9.89 (br. s, 1H), 8.55 (t, 1H), 8.06 (s, 1H), 7.74 (m, 4H), 7.52 (t, 1H), 7.23 (d, 1H), 7.15 (t, 1H), 6.49 (t, 2H), 4.45 (s, 2H), 3.95 (t, 2H), 3.88 (s, 3H), 3.69 (s, 3H), 3.30 (m, 2H), 1.70 (m, 2H), 1.60 (m, 2H), 1.44 (m, 2H)	596
97	5-(4-methoxy-3'-{*N*-[6-(3-hydroxy-2-methoxycarbonylphenoxy)hexyl] carbamoyl}-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	9.86 (br. s, 1H), 8.53 (br. t, 1H), 8.03 (s, 1H), 7.73 (m, 4H), 7.51 (t, 1H), 7.23 (d, 1H), 7.12 (t, 1H), 6.45 (m, 2H), 4.51 (s, 2H), 3.92 (t, 2H), 3.86 (s, 3H), 3.71 (s, 3H), 3.27 (m, 2H), 1.63 (m, 2H), 1.54 (m, 2H), 1.37 (m, 4H)	610

Examples 98 to 101

Using an analogous procedure to that described in Example 93, starting with 5-(4'-carboxy-4-methoxy-1,1'-biphen-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (Example 33) and the

appropriate amine (Methods 26 to 29) the following compounds were prepared in yields of 30-39%:-

Ex	Compound	^{1}H NMR (DMSO-d_6)	m/z $(M-H)^-$
98	5-(4-methoxy-4'-{*N*-[2-(3-hydroxy-2-methoxycarbonylphenoxy)ethyl]carbamoyl}-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	9.94 (br. s, 1H), 8.54 (br. t, 1H), 7.90 (m, 3H), 7.73 (m, 3H), 7.25 (d, 1H), 7.18 (t, 1H), 6.58 (d, 1H), 6.50 (d, 1H), 4.51 (s, 2H), 4.11 (t, 2H), 3.88 (s, 3H), 3.70 (s, 3H), 3.60 (m, 2H)	554
99	5-(4-methoxy-4'-{*N*-[3-(3-hydroxy-2-methoxycarbonylphenoxy)propyl]carbamoyl}-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	9.94 (br. s, 1H), 8.54 (br. t, 1H), 7.88 (m, 3H), 7.71 (m, 3H), 7.24 (d, 1H), 7.18 (t, 1H), 6.51 (t, 2H), 4.50 (s, 2H), 4.04 (t, 2H), 3.88 (s, 3H), 3.78 (s, 3H), 3.40 (m, 2H), 1.94 (m, 2H)	568
100	5-(4-methoxy-4'-{*N*-[5-(3-hydroxy-2-methoxycarbonylphenoxy)pentyl]carbamoyl}-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	9.89 (br. s, 1H), 8.47 (br. t, 1H), 7.86 (m, 3H), 7.72 (m, 3H), 7.25 (d, 1H), 7.16 (t, 1H), 6.49 (t, 2H), 4.52 (s, 2H), 3.96 (t, 2H), 3.88 (s, 3H), 3.71 (s, 3H), 3.29 (m, 2H), 1.68 (m, 2H), 1.58 (m, 2H), 1.43 (m, 2H)	596
101	5-(4-methoxy-4'-{*N*-[6-(3-hydroxy-2-methoxycarbonylphenoxy)hexyl]carbamoyl}-1,1'-biphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	9.90 (br. s, 1H), 8.45 (br. t, 1H), 7.85 (m, 3H), 7.72 (m, 3H), 7.25 (d, 1H), 7.15 (t, 1H), 6.49 (m, 2H), 4.51 (s, 2H), 3.94 (t, 2H), 3.89 (s, 3H), 3.74 (s, 3H), 3.28 (m, 2H), 1.66 (m, 2H), 1.56 (m, 2H), 1.38 (m, 4H)	610

5

Preparation of Starting Materials

The starting materials for the Examples above are either commercially available or are readily prepared by standard methods from known materials. For example the following reactions are illustrations but not limitations of the preparation of some of the starting materials used in the above reactions.

Method 1

Methyl *N*-(4-bromophenyl)glycinate

N,N-diisopropylethylamine (30 ml, 172 mmol) and methyl bromoacetate (0.95 eq, 32.68 mmol) were added to a solution of 4-bromoaniline (1 eq, 34.4 mmol) in anhydrous DMF (12 ml) under nitrogen. The solution was heated for 17 hours at 60°C before cooling in an ice bath. The cool mixture was then poured into cold water (100 ml) and refrigerated for 2 hours. Product precipitated out of solution and was filtered off, washed with water and dried under reduced pressure overnight in the presence of phosphorous pentoxide. The title compound was isolated as an off-white, brownish solid (7.768 g). ^{1}H NMR ($CDCl_3$) 7.32 (2H, d), 6.605 (2H, d), 3.93 (2H, s), 3.81 (3H, s); m/z $(M+H)^+$ 246.

Methods 2 and 3

The following compounds were obtained using an analogous procedure to that described in Method 1, using the appropriate starting material.

Method	Compound	^{1}H NMR ($CDCl_3$)	m/z $(M+H)^+$
2	Methyl *N*-(3-bromophenyl)glycinate	7.09 (1H, t), 7.96 (1H, d), 6.88 (1H, s), 6.67 (1H, d), 3.95 (2H, s), 3.82 (3H, s)	246
3	Methyl *N*-(4-methyl-1,1'-biphenyl-3-yl)glycinate	7.56 (d, 2H), 7.41 (t, 2H), 7.32 (t, 1H), 7.14 (d, 1H), 6.93 (dd, 1H), 6.68 (d, 1H), 4.24 (brs, 1H), 4.03 (s, 2H), 3.81 (s, 3H), 2.25 (s, 3H)	255

Method 4

tert-Butyl chlorosulfonylcarbamate

A solution of chlorosulfonyl isocyanate (1.2 eq, 38.16 mmol) in anhydrous dichloromethane (DCM, 20 ml) was prepared under nitrogen and cooled to 0 °C. Neat 2-

methyl-2-propanol (1.32 eq, 41.98 mmol) was added slowly under nitrogen to the cold solution and stirred for 15 minutes at 0 °C. This solution was used without further characterisation.

Method 5

Methyl *N*-(4-bromophenyl)-*N*-{[(*tert*-butoxycarbonyl)amino]sulfonyl}glycinate

Methyl *N*-(4-bromophenyl)glycinate (Method 1; 7.768 g, 1 eq, 31.8 mmol) in anhydrous DCM (90 ml) under nitrogen was cooled to 0°C. A solution of *tert*-butyl chlorosulfonylcarbamate (Method 4; 1.2 eq, 38.16 mmol) was prepared in-situ and transferred via cannula to the mixture under nitrogen. Triethylamine (2 eq, 63.6 mmol) was slowly added under nitrogen at 0°C. The ice bath was removed and the mixture stirred at ambient temperature for 1.5 hours. After the reaction was complete, the reaction mixture was extracted with water (3 x 100 ml). The organic phase was separated, dried over sodium sulfate, filtered and concentrated under reduced pressure. The title compound was isolated (11.79 g). ^{1}H NMR ($CDCl_3$) 7.555 (2H, d), 7.375 (2H, d), 7.17 (1H, s), 4.64 (2H, s), 3.76 (3H, s), 1.53 (9H, s); m/z $(M-H)^-$ 421.

Method 6

The following compound was made using an analogous procedure to that described in Method 5, using the appropriate starting materials.

Method	Compound	^{1}H NMR ($CDCl_3$)	m/z (M-H)
6	Methyl *N*-(3-bromophenyl)-*N*-{[(*tert*-butoxycarbonyl)amino]sulfonyl}glycinate	7.62 (1H, s), 7.535 (1H, d), 7.495 (1H, d), 7.31 (1H, t), 7.16 (1H, s), 4.65 (2H, s), 3.77 (3H, s), 1.54 (9H, s)	421

Method 7

5-(4-Bromophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide

Methyl *N*-(4-bromophenyl)-*N*-{[(*tert*-butoxycarbonyl)amino]sulfonyl}glycinate (Method 5; 11.79 g, 1 eq, 27.9 mmol) was deprotected by slowly adding 90% TFA-H_2O (100 ml) and stirring for 2 hours at ambient temperature. The TFA-H_2O was removed under reduced pressure and the residue was dried under high vacuum under reduced pressure for 1

hour. The concentrated compound was azeotroped 3 times with toluene to remove residual TFA-H_2O. The compound was further dried under high vacuum for 2-3 hours under reduced pressure in the presence of phosphorous pentoxide. The dried compound was then dissolved in anhydrous tetrahydrofuran (THF, 380 ml) and nitrogen was bubbled through the solution. In a separate flask, sodium hydride (60% suspension in mineral oil, 3 eq, 159 mmol) was dissolved in anhydrous THF (57 ml) and nitrogen bubbled through the solution. The sodium hydride in THF solution was slowly added to the flask containing deprotected starting material under nitrogen and stirred for 1 hour at ambient temperature. The reaction was quenched via slow addition of water (250 ml), basified with 10% sodium hydroxide to pH 14 and 400 ml ethyl acetate was added. The aqueous layer was extracted 3 x 400 ml hexane to remove mineral oil, maintaining pH 14 between washes to prevent product loss. The aqueous layer was separated and acidify to pH 1 with 10% aqueous hydrochloric acid. The acidic aqueous layer was extracted with 4 x 500 ml ethyl acetate until no product was present by TLC. The combined ethyl acetate layers were concentrated under reduced pressure to approximately 100 ml. The partially concentrated solution was dried over sodium sulfate, filtered and concentrated under reduced pressure to dryness. The product was dried overnight under high vacuum in the presence of phosphorus pentoxide. The title compound was isolated as a yellow solid (7.075 g). ^{1}H NMR ($CDCl_3$) 7.55 (2H, d), 7.23 (2H, d), 4.59 (2H, s); m/z $(M-H)^-$ 291.

Method 8

The following compound was made using an analogous procedure to that described in Method 7 using the appropriate starting materials.

Method	Compound	^{1}H NMR (CD_3OD)	m/z $(M-H)^-$
8	5-(3-bromophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.47 (1H, s), 7.25-7.34 (3H, m), 4.61 (2H, s)	291
9	5-(4-methylbiphenyl-3-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	7.76 (s, 1H), 7.64-7.62 (m, 3H), 7.48 (dd, 1H), 7.42 (d, 2H), 7.38 (td, 1H), 4.48 (s, 2H), 2.44 (s, 3H)	301

Method 10

Polystyrene/Wang/Bromoacetate resin

Diisopropylcarbodiimide (26.8 ml) was added in 5 aliquots to a solution/suspension of bromoacetic acid (47.5 g, 342 meq) at 0°C. The reaction mixture was stirred for 2.5 hours and solvent was removed by rotary evaporation at reduced pressure. The residue was taken up in dry, degassed DMF and added to a suspension of polystyrene/Wang linker resin (38.0 g, 0.9 meq/g, 34.2 meq) pre-swollen in DMF. 4-Dimethylaminopyridine (0.4 g, 3.42 meq) was then added to this solution/suspension. The entire mixture was stirred at ambient temperature for 24 hours, filtered through a coarse sintered glass funnel, and washed serially with 5 x 500 ml DMF, tetrahydrofuran, dichloromethane, and DMF. The resin was subjected to the above reaction conditions a second time using only half the number of equivalents of the reagents (solvent volumes remained the same). After 24 hours, the resin mixture was filtered and washed serially with 5 x 500 ml each of DMF, THF, dichloromethane, and diethyl ether. The resin was dried under vacuum/N_2 for 1hour followed by high vacuum at 50 °C for 2 days. Quantitative incorporation of bromoacetate was showed by elemental analysis for bromine content.

Method 11

Methyl *N*-(5-bromo-2-methoxyphenyl)glycinate

N,N-diisopropylethylamine (13.49 ml, 77.4 mmol) and methyl bromoacetate (0.95 eq, 49.0 mmol) were added to a solution of 5-bromo-2-methoxyaniline (1 eq, 51.6 mmol) in anhydrous DMF (100 ml) under nitrogen. The solution was heated for 16 hours at 60 °C before cooling to ambient temperature. DMF was removed under reduced pressure. The residue was dissolved in 500 ml of DCM, washed with 2 x 200 ml of water, was dried over sodium sulfate and was filtered and concentrated under reduced pressure. The title compound was precipitated from DCM/hexanes as an off-white, brownish solid (10.34 g). ^{1}H NMR ($CDCl_3$) 6.79 (dd, 1H), 6.63 (d, 1H), 6.56 (s, 1H), 3.91 (s, 2H), 3.84 (s, 3H), 3.80 (s, 3H); m/z $(M+H)^+$ 275.

Method 12

Methyl *N*-(5-bromo-2-methoxyphenyl)-*N*-{[(*tert*-butoxycarbonyl)amino]sulfonyl} glycinate

Methyl *N*-(5-bromo-2-methoxyphenyl)glycinate (10.30 g, 37.57 mmol, 1 eq) in anhydrous DCM (100 ml) under nitrogen was cooled to 0°C. A 0.5 M solution of *tert*-butyl

chlorosulfonylcarbamate in DCM (1.2 eq, 45.09 mmol) was added *via* syringe to the solution under nitrogen. *N,N*-diisopropylethylamine (52.60 mmol, 1.4 eq) was slowly added under nitrogen at 0°C. The ice bath was removed and the mixture was stirred at ambient temperature for 3 hours. Upon reaction completion, 150 ml aqueous saturated $NaHCO_3$ was added and the mixture was stirred for 1 hour. The organic phase was washed with water (2 x 100 ml), dried over sodium sulfate, filtered and concentrated under reduced pressure. The title compound was crystallized from DCM/hexane to afford an off-white solid (10.22 g). ^{1}H NMR ($CDCl_3$) 7.80 (d, 1H), 7.46 (d, 1H), 6.83 (d, 1H), 4.55 (s, 2H), 3.85 (s, 3H), 3.74 (s, 3H), 1.53 (s, 9H); m/z $(M-H)^-$ 452.

Method 13

Methyl *N*-(aminosulfonyl)-*N*-(5-bromo-2-methoxyphenyl)glycinate

90% TFA-H_2O (50 ml) was added slowly to methyl *N*-(5-bromo-2-methoxyphenyl)-*N*-{[(*tert*-butoxycarbonyl)amino]sulfonyl}glycinate (Method 12; 10.22 g, 22.55 mmol, 1 eq) at ambient temperature and the mixture was stirred for a further 2 hours. The TFA-H_2O was removed under reduced pressure and the residue was dried under high vacuum for 1 hour. The concentrated compound was dissolved in 200 ml DCM, washed with water (2 x 100 ml), dried over sodium sulfate, filtered, and solvent was removed under reduced pressure. The title compound was crystallized from DCM to afford a off-white crystal (6.3 g) ^{1}H NMR ($CDCl_3$) 7.74 (d, 1H), 7.44 (dd, 1H0, 6.84 (d, 1H0, 5.08 (s, 2H), 4.33 (s, 2H), 3.86 (s, 3H0, 3.77 (s, 3H); m/z $(M-H)^-$ 352.

Method 14

5-(5-Bromo-2-methoxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide

Sodium hydride (60% suspension in mineral oil (1.08g, 27.1 mmol, 2 eq) was suspended in anhydrous THF (200 ml) and the solution was degassed with nitrogen. A solution of methyl *N*-(aminosulfonyl)-*N*-(5-bromo-2-methoxyphenyl)glycinate (Method 13, 4.78 g, 13.53 mmol, 1 eq) in anhydrous THF (300 ml) was added dropwise over 2 hours, and the mixture was stirred for 1 hour at ambient temperature. The reaction was quenched by slow addition of water (10 ml). The solvent was removed under reduced pressure. The residue was dissolved in water (200 ml), extracted with ether (2 x 100 ml) to remove the mineral oil. The aqueous layer was separated, acidified to pH 1 with 10 % aqueous hydrochloric acid and extracted with ethyl acetate (3 x 40 ml) until no product was present in aqueous layer. The

pH was maintained at 1 between each extraction. The organic extracts were combined and concentrated under reduced pressure. The title compound was crystallized from DCM to afford an off-white solid (3.5 g). ^{1}H NMR (DMSO-d_6): 7.66 (s, 1H), 7.47 (d, 1H), 7.10 (d, 1H), 4.42 (s, 2H), 3.81 (s, 3H). m/z, $(M-H)^-$ 320.

Method 15

5-[5-(Dihydroxyboryl)-methoxyphenyl]-1,2,5-thiadiazolidin-3-one-1,1-dioxide

5-(5-Bromo-2-methoxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (Method 14, 642 mg, 2 mmol) was dissolved in 40 mL dry THF under an inert atmosphere, cooled to –78 °C and BuMgCl (2 M solution in THF, 1.050 mL, 2.1 mmol) was added via a syringe. After 10 min, *t*-BuLi (1.7 M solution in pentane, 2.6 mL, 4.4 mmol) was added. The mixture was stirred for 10 min at –78 °C and trimethylborate (1.817 mL, 16 mmol) was added. The cooling bath was removed and the mixture was allowed to warm to room temperature. After 30 min at room temperature, a 2 N aqueous solution of HCl (10 mL, 20 mmol) was added and stirred for 20 min. Saturated aqueous ammonium chloride(50 mL) was added, the mixture was extracted with ethyl acetate (5 x 30 mL). The combined organic layers were dried over $MgSO_4$ to afford a solid that was purified by reversed-phase HPLC (Phenomenex Synergi Polar RP column, 21.2 x 100 mm (4µm particles), 5-95% ACN with 0.1% TFA, 20 mL/min, 25°C, 16.3 min run time, scanning at 220 to 400 nM) to give the title product (95 mg). ^{1}H NMR (DMSO-d_6): 7.79 (m, 2H), 7.11 (d, 1H), 4.45 (s, 2H), 3.81 (s, 3H); m/z $(\bar{M}\bar{H})$ 285

Method 16

5-[2-Methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,2,5-thiadiazolidin-3-one 1,1-dioxide

To a degassed solution of 5-(5-iodo-2-methoxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (Method 32, 5.14 g, 13.97 mmol), bis(pinacolato)boron (7.12 g, 27.9 mmol) and potassium acetate (4.13 g, 41.9 mmol) in DMF (70 ml) was added [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) complex with dichloromethane (1:1) (1.025 g, 1.40 mmol) and the mixture heated for 16 hours. After cooling the mixture was concentrated to ~30 ml then partitioned between Et_2O (100 ml) and 1M $NaHCO_3$ aq. (100 ml). The aqueous was acidified with conc. HCl aq. (~10 ml) and then extracted with EtOAc (500 ml). The organic was dried ($MgSO_4$), decolourised with charcoal, filtered and evaporated to leave a pale yellow, clear gum. Trituration with Et_2O (30 ml) then filtration,

washing with Et_2O (20 ml) then hexane (20 ml) gave the title compound as a pale brown solid. Yield (3.40 g, 66%). ^1H nmr (DMSO-d_6) 7.96 (s, 1H), 7.71 (d, 1H), 7.67 (dd, 1H), 7.17 (d, 1H), 4.48 (s, 2H), 3.86 (s, 3H), 2.90 (s, 3H), 2.74 (s, 3H), 1.30 (s, 12H); m/z $(M-H)^-$ 367 (as a 1:1 adduct with DMF).

Method 17

Methyl 2-[3-(4-bromophenyl)propoxy]-6-hydroxybenzoate

Methyl 2,6-dihydroxybenzoate (1.002 g, 5.96 mmol), 3-(4-bromophenyl)propanol (1.002 g, 4.66 mmol) and polymer supported PPh_3 (2.34 mmol/g; 8.76g, 20.50 mmol) were suspended in CH_2Cl_2 (100 ml) under an inert atmosphere and cooled to 0 °C. Diethyl azodicarboxylate (1.10 ml, 6.99 mmol) was added and the mixture allowed to warm to room temperature and stirred for 18 hours. The solid was filtered off and washed with DCM (100 ml) and the solution evaporated to give an off white solid. Purification by chromatography through silica, eluent Et_2O: Hexane (1:4) gave the title compound as a white solid. Yield (381mg, 22%) ($CDCl_3$) 11.43 (s, 1H), 7.43-7.38 (m, 2H), 7.29 (t, 1H), 7.10-7.06 (m, 2H), 6.58 (d, 1H), 6.34 (d, 1H), 3.96 (s, 3H), 3.94 (t, 2H), 2.82 (t, 2H), 2.13-2.05 (m, 2H); m/z $(M-H)^-$ 363

The following intermediates were prepared in a similar manner to that described above: -

Method	Compound	NMR ($CDCl_3$)	M/z $(M-H)^-$
18	Methyl 2-hydroxy-6-[(4-iodobenzyl)oxy]benzoate	11.44 (s, 1H), 7.75-7.70 (m, 2H), 7.32 (t, 1H), 7.22 (d, 1H), 6.63 (d, 1H), 6.44 (d, 1H), 5.05 (s, 2H), 3.94 (s, 3H);	383
19	Methyl 2-[2-(3-bromophenyl)ethoxy]-6-hydroxybenzoate	11.44 (s, 1H), 7.52 (s, 1H), 7.39-7.36 (m, 1H), 7.32-7.15 (m, 4H), 6.59 (d, 1H), 6.37 (d, 1H), 4.20 (t, 2H), 3.92 (s, 3H), 3.09 (t, 2H)	349

20	Methyl 2-[2-(4-bromophenyl)ethoxy]-6-hydroxybenzoate	11.41 (s, 1H), 7.46-7.41 (m, 2H), 7.29 (t, 1H), 7.21-7.16 (m, 2H), 6.58 (d, 1H), 6.37 (d, 1H), 4.19 (t, 2H), 3.88 (s, 3H), 3.08 (t, 2H)	349
21	Methyl 2-[3-(3-bromophenyl)propoxy]-6-hydroxybenzoate	11.44 (s, 1H), 7.38-7.25 (m, 3H), 7.18-7.11 (m, 2H), 6.59 (d, 1H), 6.35 (d, 1H), 3.98 (t, 2H), 3.97 (s, 3H), 2.84 (t, 2H), 2.15-2.07 (m, 2H)	363

Method 22:

Methyl 2-({6-[(*tert*-butoxycarbonyl)amino]hexyl}oxy)-6-hydroxybenzoate

Methyl 2,6-dihydroxybenzoate (0.454 g, 2.7 mmol, 1.0 eq.), triphenylphosphine (0.787 g, 3.0 mmol, 1.1 eq.) and *tert*-butyl (6-hydroxyhexyl)carbamate were added to the reaction flask and this was degassed using three evacuation/nitrogen fill cycles. THF (10 mL) was added and the whole cooled in an ice-water bath. DEAD (0.42 mL, 2.7 mmol, 1.0 eq.) was added dropwise and the yellow solution was allowed to warm to ambient temperature and stirred overnight. The solvent was removed under reduced pressure and toluene (10 mL) added to the residue. After removing the precipitate by filtration, the filtrate was evaporated under reduced pressure and the residue purified by column chromatography (isohexane-EtOAc, 9:1) to afford the title compound as clear oil which solidifies to a colourless solid on standing (0.523 g, 67% yield). ^{1}H NMR (DMSO-d_6): 9.86 (s, 1H), 7.13 (t, 1H), 6.70 (br. s, 1H), 6.45 (m, 2H), 3.91 (t, 2H), 3.71 (s, 3H), 2.87 (m, 2H), 1.59 (m, 2H), 1.29 (m, 15H); m/z $(M+Na)^+$ 390.

Methods 23 to 25

Using an analogous procedure to that described in Method 22, but starting with methyl 2,6-dihydroxybenzoate and the appropriate alcohol the following compounds were prepared:-

Method	Compound	^{1}H NMR ($CDCl_3$)	m/z $(M+Na)^+$
23	Methyl 2-({2-[(*tert*-butoxycarbonyl)amino]ethyl} oxy)-6-hydroxybenzoate	7.3 (t, 1H), 6.6 (d, 1H), 6.3 (d, 1H), 5.2 (br. s, 1H), 4.0 (t, 2H), 3.9 (s, 3H), 3.5 (m, 2H), 1.4 (s, 9H)	-
24	Methyl 2-({3-[(*tert*-butoxycarbonyl)amino]propyl}oxy)-6-hydroxybenzoate	7.3 (t, 1H), 6.6 (d, 1H), 6.4 (d, 1H), 5.2 (br. s, 1H), 4.1 (t, 2H), 4.0 (s, 3H), 3.4 (m, 2H), 2.0 (m, 2H), 1.4 (s, 9H)	-
25	Methyl 2-({5-[(*tert*-butoxycarbonyl)amino]pentyl}oxy)-6-hydroxybenzoate	(DMSO) 9.87 (s, 1H), 7.13 (t, 1H), 6.71 (br. s, 1H), 6.46 (m, 2H), 3.90 (t, 2H), 3.72 (s, 3H), 2.89 (m, 2H), 1.61 (m, 2H), 1.35 (m, 13H)	376

Method 26: Methyl 2-(2-aminoethoxy)-6-hydroxybenzoate Hydrochloride

Methyl 2-({2-[(*tert*-butoxycarbonyl)amino]ethyl}oxy)-6-hydroxybenzoate (Method 23) (0.100 g, 0.32 mmol, 1 eq.) was charged to the reaction flask and cooled to 0 °C. A solution of HCl in dioxane (4 M, 0.5 mL, 1.92 mmol, 6 eq.) was then added, the reaction allowed to reach ambient temperature and stirred for a further 3.5 hours. Solvent evaporated under reduced pressure and the residue dried under vacuum to afford the title compound as a colourless solid (0.075 g, 95% yield). ^{1}H NMR (DMSO-d_6): 10.10 (br. s, 1H), 8.13 (br. s, 3H), 7.19 (t, 1H), 6.56 (t, 2H), 4.16 (t, 2H), 3.76 (s, 3H), 3.11 (br. m, 2H); m/z $(M+Na)^+$ 234.

Methods 27 to 29

Using an analogous procedure to that described in Method 26, but starting with the appropriate protected amine (Methods 24, 25 and 22 respectively) the following compounds were prepared in yields of 72-93%:-

Method	Compound	^{1}H NMR (DMSO-d_6)	m/z $(M+H)^+$
27	Methyl 2-(3-aminopropoxy)-6-hydroxybenzoate hydrochloride	10.03 (s, 1H), 7.94 (br. s, 3H), 7.19 (t, 1H), 6.52 (t, 2H), 4.06 (t, 2H), 3.77 (s, 3H), 2.89 (m, 2H), 1.97 (m, 2H)	226
28	Methyl 2-[(5-aminopentyl)oxy]-6-hydroxybenzoate hydrochloride	9.97 (s, 1H), 7.90 (br. s, 3H), 7.16 (t, 1H), 6.51 (t, 2H), 3.95 (t, 2H), 3.75 (s, 3H), 2.77 (t, 2H), 1.67 (m, 2H), 1.58 (m, 2H), 1.42 (m, 2H)	254
29	Methyl 2-[(6-aminohexyl)oxy]-6-hydroxybenzoate hydrochloride	9.96 (s, 1H), 7.91 (br. s, 3H), 7.15 (t, 1H), 6.50 (t, 2H), 3.95 (t, 2H), 3.74 (s, 3H), 2.75 (m, 2H), 1.63 (m, 2H), 1.55 (m, 2H), 1.35 (m, 4H)	268

Method 30: Methyl *N*-(5-iodo-2-methoxyphenyl)glycinate

5-Iodo-2-methoxyaniline (24.905 g, 100 mmol) was dissolved in dry DMF (50 mL), DIPEA (26.1 mL, 150 mmol) was added under N_2 followed by methyl bromoacetate (9.5 mL, 100 mmol). The mixture was stirred on an oil bath heated at 65 °C for 16 h. The volatiles were evaporated under high vacuum and the remaining oil was partitioned between EtOAc (120 mL) and water (50 mL). The organic layer was washed with water (2 x 50 mL), was dried ($MgSO_4$) and solvent evaporated to afford an oil. The oil was taken up in methanol (30 mL) and dissolved by bringing the solution to a boil. After cooling to 10 °C, the solid was filtered off and was washed with cold MeOH (30 mL) on the filter and dried in the air (in the dark) to afford the title compound as light yellow prisms (24.57 g , 77% yield). ^{1}H NMR ($CDCl_3$): 6.98 (d, 1H), 6.70 (s, 1H), 6.50 (d, 1H), 4.83 (br. s, 1H), 3.89 (d, 2H), 3.82 (s, 3H). ^{13}C NMR ($CDCl_3$): 171.1, 146.9, 138.5, 126.0, 118.1, 111.4, 83.7, 55.5, 52.2, 45.1.

Method 31: Methyl *N*-(aminosulfonyl)-*N*-(5-iodo-2-methoxyphenyl)glycinate

Methyl *N*-(5-iodo-2-methoxyphenyl) glycinate (Method 30, 16.056 g, 50 mmol) was dissolved in dry DCM (60 mL) under N_2 and DIPEA was added (8.9 mL, 51 mmol). The solution was cooled to 0 °C and a 0.5 M solution of *N*-Boc-sulfamoyl chloride in DCM freshly prepared [1.2 eq tBuOH (66 mmol, in DCM 30 mL) was added dropwise to $ClSO_2NCO$ (55 mmol, in DCM 70 mL) at 0-10 °C and allowed to warm to ambient temperature over 30 min] was added via a syringe (110 mL, 55 mmol). After the addition was complete the cooling bath was removed and the solution was stirred for 3 h. Sodium bicarbonate saturated aqueous solution was added (50 mL) and stirred for 30 min, was separated and the organic layer was washed with water (2 x 50 mL), dried ($MgSO_4$) and solvent evaporated to give a thick oil which crystallized upon standing into a glassy mass. The solid was treated with TFA/water (9/1 v/v; 100 mL) and stirred at ambient temperature in the dark for 1h. The volatiles were evaporated under reduced pressure and the remaining oil was partitioned between DCM (200 mL) and saturated sodium bicarbonate aqueous solution (200 mL) and the heterogenous mixture was stirred for 1h. The organic layer was separated and was washed with water (2 x 50 mL), dried (MgSO4) and solvent evaporated. The remaining tan solid was recrystallized from MeOH to afford the title compound as colourless crystals (15.258 g, 76% yield). ^{1}H NMR (CD_3CN): 7.83 (d, 1H), 7.66 (dd, 1H), 6.88 (d, 1H), 5.45 (br. s, 2H), 4.27 (s, 2H), 3.84 (s, 3H), 3.69 (s, 3H).

Method 32: 5-(5-Iodo-2-methoxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide

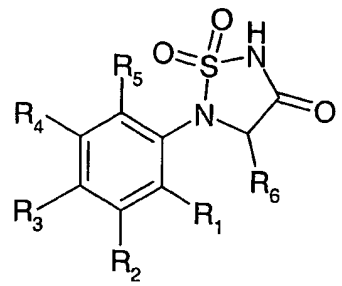
Methyl *N*-(aminosulfonyl)-*N*-(5-iodo-2-methoxyphenyl)glycinate (Method 31, 14.406 g, 36 mmol) was dissolved in dry THF (360 mL) under N_2, and was cooled to 0 °C on an ice-water bath. Potassium *tert*-butoxide in *t*-butanol (1 M, 40 mL, 40 mmol) was added slowly (10 min) *via* a syringe. Once the addition was complete the cooling bath was removed and the milky suspension was stirred at room temperature and shielded from light for 1 h. The volatiles were removed under reduced pressure and the remaining solid was suspended in water (200 mL). Aqueous HCl solution was added (1 N, 50 mL, 50 mmol) followed by addition of EtOAc (50 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (4 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and solvent was evaporated to afford 13.20 g crude material (light brown). Crystallization from MeOH afforded 10.31 g large prisms which contained 0.75 molecules MeOH per molecule of product. The solid was dissolved in acetonitrile and solvent removed to afford the title

compound as a colourless powder white powder (8.753 g, 69% yield). ^{1}H NMR (DMSO-d_6): 11.93 (br. s, 1H), 7.72 (d, 1H), 7.64 (dd, 1H), 6.97 (d, 1H), 4.47 (s, 2H), 3.79 (s, 3H). ^{13}C NMR (DMSO-d_6): 169.9, 152.9, 137.7, 136.7, 126.0, 115.6, 82.3, 56.1, 54.7.

The compound of Method 32 shows PTP1B inhibitory activity and provides a further aspect of the invention.

Claims

1. A compound of formula (I):



(I)

wherein

R_1 is hydrogen, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylthio, halogeno, halogeno(1-6C)alkyl, halogeno(1-6C)alkoxy, halogeno(1-6C)alkylthio, hydroxy(1-6C)alkoxy, dihydroxy(1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy, aryloxy, aryl(1-6C)alkoxy, aryloxy(1-6C)alkoxy, heteroaryl(1-6C)alkoxy, heteroaryloxy, heteroaryloxy(1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkylthio, (1-6C)alkylthio(1-6C)alkoxy, (1-6C)alkylsulfinyl(1-6C)alkoxy, (1-6C)alkylsulfonyl(1-6C)alkoxy, aryl(1-6C)alkylthio, aryloxy(1-6C)alkylthio, heteroaryl(1-6C)alkylthio, heteroaryloxy(1-6C)alkylthio, (1-6C)alkoxy(1-6C)alkyl, aryloxy(1-6C)alkyl, heteroaryloxy(1-6C)alkyl, (1-6C)alkylthio(1-6C)alkyl, arylthio(1-6C)alkyl, heteroarylthio(1-6C)alkyl, (1-6)alkylsulfinyl(1-6C)alkyl, arylsulfinyl(1-6C)alkyl, (1-6C)alkylsulfonyl(1-6C)alkyl, arylsulfonyl(1-6C)alkyl, carbamoyl(1-6C)alkoxy, carbamoyl(1-6C)alkyl, (2-6C)alkanoylamino(1-6C)alkoxy, (2-6C)alkanoylamino(1-6C)alkyl, aryl(1-6C)alkyl, heteroaryl(1-6C)alkyl, hydroxy(1-6C)alkyl, dihydroxy(2-6C)alkyl, amino(1-6C)alkyl, carboxy(1-6C)alkyl, sulfamoyl(1-6C)alkyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (2-8C)alkenyl, (2-8C)alkynyl, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, *N*-(1-6C)alkylcarbamoyl, *N*,*N*-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, *N*-(1-6C)alkyl-(2-6C)alkanoylamino, *N*-(1-6C)alkylsulphamoyl,

N,*N*-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and *N*-(1-6C)alkyl-(1-6C)alkanesulphonylamino;

or R_1 is a group of the formula $-Z-(CHR_7)_m-X-NR_8R_9$ wherein

m is 1, 2 or 3;

R_7 is hydrogen, (1-6C)alkyl, aryl, heteroaryl, aryl(1-6C)alkyl, hydroxy or (1-6C)alkoxy;

X is –C(O)-, -S(O)- or –$S(O)_2$-; and R_8 and R_9 are independently selected from hydrogen, (1-6C)alkyl, aryl and heteroaryl; or R_8 and R_9 together with the nitrogen atom to which they are attached form a heterocyclic ring; or X is a covalent bond, R_8 is hydrogen, (1-6C)alkyl or aryl, and R_9 is $–COR_{10}$ or SO_2R_{10} wherein R_{10} is (1-6C)alkyl, aryl, heteroaryl, aryl(1-6C)alkyl or heteroaryl(1-6C)alkyl; and

Z is a covalent bond, O or S; with the proviso that no two heteroatoms are attached through single bonds to the same carbon atom;

R_2 is selected from H, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylthio and halogeno;

or R_1 and R_2 together with the carbon atoms to which they are attached form a 5-7 membered carbocyclic or heterocyclic ring;

R_3 and R_4 are selected such that

(v) R_3 is hydrogen, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylthio or halogeno and R_4 is aryl, biaryl, heteroaryl, (2-6C)alkynyl, (3-7C)cycloalkyl, arylcarbonyl, heteroarylcarbonyl, aryl(2-6C)alkenyl, aryl(2-6C)alkynyl or heteroaryl(2-6C)alkenyl;

or

(vi) R_4 is hydrogen, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylthio or halogeno and R_3 is aryl, biaryl, heteroaryl, (2-6C)alkynyl, (3-7C)cycloalkyl, arylcarbonyl, heteroarylcarbonyl, aryl(2-6C)alkenyl, aryl(2-6C)alkynyl or heteroaryl(2-6C)alkenyl;

R_5 is hydrogen, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylthio, halo(1-6C)alkyl or halogeno;

R_6 is hydrogen or (1-6C)alkyl;

and wherein any aryl, biaryl or heteroaryl group within or part of the definition of R_1, R_3 or R_4 is unsubstituted or bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, *N*-(1-6C)alkylcarbamoyl, *N*,*N*-di-[(1-6C)alkyl]carbamoyl, *N*-pyrrolidinylcarbonyl, *N*-piperidinylcarbonyl, *N*-(1-6C)alkylcarbamoyloxy(1-6C)alkyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, *N*-(1-6C)alkyl-(2-6C)alkanoylamino, *N*-(1-6C)alkylsulphamoyl, *N*,*N*-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino, *N*-(1-6C)alkyl-

(1-6C)alkanesulphonylamino, (1-6C)alkoxy(1-6C)alkyl, (1-6C)alkoxy(1-6C)alkoxy, hydroxy(1-6C)alkyl, carboxy(1-6C)alkyl, aryl(1-6C)alkyl, heteroaryl(1-6C)alkyl, aryloxy(1-6C)alkyl, heteroaryloxy(1-6C)alkyl, aryloxy(1-6C)alkylcarbamoyl, aryloxy(1-6C)alkylsulphamoyl, aryl(1-6C)alkoxy, heteroaryl(1-6C)alkoxy, aryloxy(1-6C)alkoxy, heteroaryloxy(1-6C)alkoxy, aryloxy and heteroaryloxy, and wherein an aryl or heteroaryl moiety of said last twelve groups is unsubstituted or bears 1, 2 or 3 substituents, which may be the same or different; or two adjacent carbons of said aryl, biaryl or heteroaryl group may be linked by a divalent radical of formula $-O(CH_2)_{1-4}O-$;
or a pharmaceutically acceptable salt thereof.

2. A compound of the formula (I) as claimed in Claim 1, or a pharmaceutically acceptable salt thereof, wherein

R_1 is hydrogen, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylthio, halogeno, halogeno(1-6C)alkyl, halogeno(1-6C)alkoxy, halogeno(1-6C)alkylthio, hydroxy(1-6C)alkoxy, dihydroxy(1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy, aryloxy, aryl(1-6C)alkoxy, aryloxy(1-6C)alkoxy, heteroaryl(1-6C)alkoxy, heteroaryloxy(1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkylthio, (1-6C)alkylthio(1-6C)alkoxy, (1-6C)alkylsulfinyl(1-6C)alkoxy, (1-6C)alkylsulfonyl(1-6C)alkoxy, aryl(1-6C)alkylthio, aryloxy(1-6C)alkylthio, heteroaryl(1-6C)alkylthio, heteroaryloxy(1-6C)alkylthio, (1-6C)alkoxy(1-6C)alkyl, aryloxy(1-6C)alkyl, heteroaryloxy(1-6C)alkyl, (1-6C)alkylthio(1-6C)alkyl, arylthio(1-6C)alkyl, heteroarylthio(1-6C)alkyl, (1-6)alkylsulfinyl(1-6C)alkyl, arylsulfinyl(1-6C)alkyl, (1-6C)alkylsulfonyl(1-6C)alkyl, arylsulfonyl(1-6C)alkyl, carbamoyl(1-6C)alkoxy, carbamoyl(1-6C)alkyl, (2-6C)alkanoylamino(1-6C)alkoxy, (2-6C)alkanoylamino(1-6C)alkyl, aryl(1-6C)alkyl, heteroaryl(1-6C)alkyl, hydroxy(1-6C)alkyl, amino(1-6C)alkyl, carboxy(1-6C)alkyl, sulfamoyl(1-6C)alkyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (2-8C)alkenyl, (2-8C)alkynyl, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, *N*-(1-6C)alkylcarbamoyl, *N*,*N*-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, *N*-(1-6C)alkyl-(2-6C)alkanoylamino, *N*-(1-6C)alkylsulphamoyl, *N*,*N*-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and *N*-(1-6C)alkyl-(1-6C)alkanesulphonylamino;
or R_1 is a group of the formula $-Z-(CHR_7)_m-X-NR_8R_9$ wherein
m is 1, 2 or 3;

R_7 is hydrogen, (1-6C)alkyl, aryl, heteroaryl, aryl(1-6C)alkyl, hydroxy or (1-6C)alkoxy;

X is –C(O)-, -S(O)- or $–S(O)_2$-; and R_8 and R_9 are independently selected from hydrogen, (1-6C)alkyl, aryl and heteroaryl; or R_8 and R_9 together with the nitrogen atom to which they are attached form a heterocyclic ring; or X is a covalent bond, R_8 is hydrogen, (1-6C)alkyl or aryl, and R_9 is $–COR_{10}$ or SO_2R_{10} wherein R_{10} is (1-6C)alkyl, aryl, heteroaryl, aryl(1-6C)alkyl or heteroaryl(1-6C)alkyl; and

Z is a covalent bond, O or S; with the proviso that no two heteroatoms are attached through single bonds to the same carbon atom;

R_2 is H or (1-6C)alkyl;

or R_1 and R_2 together with the carbon atoms to which they are attached form a 5-7 membered carbocyclic or heterocyclic ring;

R_3 and R_4 are selected such that

(vii) R_3 is hydrogen, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylthio or halogeno and R_4 is aryl, biaryl, heteroaryl, (3-7C)cycloalkyl, arylcarbonyl, heteroarylcarbonyl, aryl(2-6C)alkenyl or heteroaryl(2-6C)alkenyl;

or

(viii) R_4 is hydrogen, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylthio or halogeno and R_3 is aryl, biaryl, heteroaryl, (3-7C)cycloalkyl, arylcarbonyl, heteroarylcarbonyl, aryl(2-6C)alkenyl or heteroaryl(2-6C)alkenyl;

R_5 is hydrogen, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylthio or halogeno;

R_6 is hydrogen or (1-6C)alkyl;

and wherein any aryl, biaryl or heteroaryl group within or part of the definition of R_1, R_3 or R_4 is unsubstituted or bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, *N*-(1-6C)alkylcarbamoyl, *N*,*N*-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, *N*-(1-6C)alkyl-(2-6C)alkanoylamino, *N*-(1-6C)alkylsulphamoyl, *N*,*N*-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino, *N*-(1-6C)alkyl-(1-6C)alkanesulphonylamino, (1-6C)alkoxy(1-6C)alkyl, (1-6C)alkoxy(1-6C)alkoxy, hydroxy(1-6C)alkyl, aryl(1-6C)alkyl, heteroaryl(1-6C)alkyl, aryloxy(1-6C)alkyl, heteroaryloxy(1-6C)alkyl, aryl(1-6C)alkoxy, heteroaryl(1-6C)alkoxy, aryloxy(1-6C)alkoxy,

heteroaryloxy(1-6C)alkoxy, aryloxy and heteroaryloxy, and wherein an aryl or heteroaryl moiety of said last ten groups is unsubstituted or bears 1, 2 or 3 substituents, which may be the same or different; or two adjacent carbons of said aryl, biaryl or heteroaryl group may be linked by a divalent radical of formula $-O(CH_2)_{1-4}O-$.

3. A compound of the formula (I) as claimed in Claim 1 or Claim 2, or a pharmaceutically-acceptable salt thereof, wherein
R_1 is (1-6C)alkoxy, hydroxy-(1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy, (1-6C)alkylthio(1-6C)alkoxy, (1-6C)alkylsulfinyl(1-6C)alkoxy, (1-6C)alkylsulfonyl(1-6C)alkoxy, aryl(1-6C)alkoxy, fluoro(1-6C)alkoxy, carbamoyl(1-6C)alkoxy, (2-6C)alkanoylamino(1-6C)alkoxy, (1-6C)alkoxy-(1-6C)alkyl, aryloxy(1-6C)alkyl, (1-6C)alkylsulfinyl(1-6C)alkyl, (1-6C)alkylsulfonyl(1-6C)alkyl, (2-6C)alkanoylamino(1-6C)alkyl or carbamoyl(1-6C)alkyl.

4. A compound of the formula (I) as claimed in any one of Claims 1 to 3, or a pharmaceutically-acceptable salt thereof, wherein R_3 is unsubstituted aryl or substituted aryl.

5. A compound of the formula (I) as claimed in any one of Claims 1 to 3, or a pharmaceutically-acceptable salt thereof, wherein R_4 is unsubstituted aryl or substituted aryl.

6. A compound of the formula (I) as claimed in any one of the preceding claims, or a pharmaceutically-acceptable salt thereof, wherein R_2 is hydrogen.

7. A compound of the formula (I) as claimed in any one of the preceding claims, or a pharmaceutically-acceptable salt thereof, wherein R_5 is hydrogen.

8. A compound of the formula (I) as claimed in any one of the preceding claims, or a pharmaceutically-acceptable salt thereof, wherein R_6 is hydrogen.

9 A compound of the formula (I) as claimed in Claim 1, or a pharmaceutically acceptable salt thereof wherein R_1 is (1-6C)alkoxy, hydroxy-(1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy, (1-6C)alkylthio(1-6C)alkoxy, (1-6C)alkylsulfinyl(1-6C)alkoxy, (1-6C)alkylsulfonyl(1-6C)alkoxy, aryl(1-6C)alkoxy, fluoro(1-6C)alkoxy, carbamoyl(1-6C)alkoxy, (2-6C)alkanoylamino(1-6C)alkoxy, (1-6C)alkoxy-(1-6C)alkyl, aryloxy(1-

6C)alkyl, (1-6C)alkylsulfinyl(1-6C)alkyl, (1-6C)alkylsulfonyl(1-6C)alkyl, (2-6C)alkanoylamino(1-6C)alkyl, carbamoyl(1-6C)alkyl; R_2, R_4, R_5 and R_6 are each hydrogen; R_3 is unsubstituted phenyl or phenyl bearing 1, 2 or 3 substituents, which may be the same or different independently selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, *N*-(1-6C)alkylcarbamoyl, *N*,*N*-di-[(1-6C)alkyl]carbamoyl, *N*-pyrrolidinylcarbonyl, *N*-piperidinylcarbonyl, *N*-(1-6C)alkylcarbamoyloxy(1-6C)alkyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, *N*-(1-6C)alkyl-(2-6C)alkanoylamino, *N*-(1-6C)alkylsulphamoyl, *N*,*N*-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino, *N*-(1-6C)alkyl-(1-6C)alkanesulphonylamino, (1-6C)alkoxy(1-6C)alkyl, (1-6C)alkoxy(1-6C)alkoxy, hydroxy(1-6C)alkyl, carboxy(1-6C)alkyl, aryl(1-6C)alkyl, heteroaryl(1-6C)alkyl, aryloxy(1-6C)alkyl, heteroaryloxy(1-6C)alkyl, aryloxy(1-6C)alkylcarbamoyl, aryloxy(1-6C)alkylsulphamoyl, aryl(1-6C)alkoxy, heteroaryl(1-6C)alkoxy, aryloxy(1-6C)alkoxy, heteroaryloxy(1-6C)alkoxy, aryloxy and heteroaryloxy, and wherein an aryl or heteroaryl moiety of said last twelve groups is unsubstituted or bears 1, 2 or 3 substituents, which may be the same or different; or two adjacent carbons of said aryl, biaryl or heteroaryl group may be linked by a divalent radical of formula $-O(CH_2)_{1-4}O-$

10. A compound of the formula (I) as claimed in Claim 1, or a pharmaceutically acceptable salt thereof wherein R_1 is (1-6C)alkoxy, hydroxy-(1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy, (1-6C)alkylthio(1-6C)alkoxy, (1-6C)alkylsulfinyl(1-6C)alkoxy, (1-6C)alkylsulfonyl(1-6C)alkoxy, aryl(1-6C)alkoxy, fluoro(1-6C)alkoxy, carbamoyl(1-6C)alkoxy, (2-6C)alkanoylamino(1-6C)alkoxy, (1-6C)alkoxy-(1-6C)alkyl, aryloxy(1-6C)alkyl, (1-6C)alkylsulfinyl(1-6C)alkyl, (1-6C)alkylsulfonyl(1-6C)alkyl, (2-6C)alkanoylamino(1-6C)alkyl, carbamoyl(1-6C)alkyl; R_2, R_3, R_5 and R_6 are each hydrogen; R_4 is unsubstituted phenyl or phenyl bearing 1, 2 or 3 substituents, which may be the same or different independently selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, *N*-(1-6C)alkylcarbamoyl, *N*,*N*-di-[(1-6C)alkyl]carbamoyl, *N*-pyrrolidinylcarbonyl, *N*-

piperidinylcarbonyl, *N*-(1-6C)alkylcarbamoyloxy(1-6C)alkyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, *N*-(1-6C)alkyl-(2-6C)alkanoylamino, *N*-(1-6C)alkylsulphamoyl, *N*,*N*-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino, *N*-(1-6C)alkyl-(1-6C)alkanesulphonylamino, (1-6C)alkoxy(1-6C)alkyl, (1-6C)alkoxy(1-6C)alkoxy, hydroxy(1-6C)alkyl, carboxy(1-6C)alkyl, aryl(1-6C)alkyl, heteroaryl(1-6C)alkyl, aryloxy(1-6C)alkyl, heteroaryloxy(1-6C)alkyl, aryloxy(1-6C)alkylcarbamoyl, aryloxy(1-6C)alkylsulphamoyl, aryl(1-6C)alkoxy, heteroaryl(1-6C)alkoxy, aryloxy(1-6C)alkoxy, heteroaryloxy(1-6C)alkoxy, aryloxy and heteroaryloxy, and wherein an aryl or heteroaryl moiety of said last twelve groups is unsubstituted or bears 1, 2 or 3 substituents, which may be the same or different; or two adjacent carbons of said aryl, biaryl or heteroaryl group may be linked by a divalent radical of formula $-O(CH_2)_{1-4}O-$.

11. A compound of the formula (I) as claimed in Claim 9 or Claim 10, or a pharmaceutically acceptable salt thereof wherein R_1 is (1-4C)alkoxy.

12. A compound of the formula (I) as claimed in Claim 9, or a pharmaceutically acceptable salt thereof wherein optional substituents on a phenyl ring in R_3 are independently selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (1-6C)alkoxy, (1-6C)alkylthio, *N*,*N*-di-[(1-6C)alkyl]carbamoyl, *N*-pyrrolidinylcarbonyl, *N*-piperidinylcarbonyl, *N*-(1-6C)alkylcarbamoyloxy(1-6C)alkyl, (2-6C)alkanoyl, (2-6C)alkanoylamino, (1-6C)alkoxy(1-6C)alkyl, carboxy(1-6C)alkyl, aryloxy(1-6C)alkyl, aryloxy(1-6C)alkylcarbamoyl, aryloxy(1-6C)alkylsulphamoyl, aryl(1-6C)alkoxy and aryloxy(1-6C)alkoxy, and wherein an aryl or heteroaryl moiety of said last five groups is unsubstituted or bears 1 or 2 substituents, which may be the same or different; or two adjacent carbons of said aryl, biaryl or heteroaryl group may be linked by a divalent radical of formula $-O(CH_2)_{1-4}O-$.

13. A compound of the formula (I) as claimed in Claim 10, or a pharmaceutically acceptable salt thereof wherein optional substituents on a phenyl ring in R_4 are independently selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (1-6C)alkoxy, (1-6C)alkylthio, *N*,*N*-di-[(1-6C)alkyl]carbamoyl, *N*-pyrrolidinylcarbonyl, *N*-piperidinylcarbonyl, *N*-(1-6C)alkylcarbamoyloxy(1-6C)alkyl, (2-6C)alkanoyl, (2-6C)alkanoylamino, (1-6C)alkoxy(1-6C)alkyl, carboxy(1-6C)alkyl, aryloxy(1-

6C)alkyl, aryloxy(1-6C)alkylcarbamoyl, aryloxy(1-6C)alkylsulphamoyl, aryl(1-6C)alkoxy and aryloxy(1-6C)alkoxy, and wherein an aryl or heteroaryl moiety of said last five groups is unsubstituted or bears 1 or 2 substituents, which may be the same or different; or two adjacent carbons of said aryl, biaryl or heteroaryl group may be linked by a divalent radical of formula $-O(CH_2)_{1-4}O-$.

14. A compound of the formula (I) as claimed in Claim 1, or a pharmaceutically acceptable salt thereof, wherein R_4 is hydrogen and R_3 is aryl bearing 1 substituent independently selected from (i) aryl(1-6C)alkyl; (ii) aryloxy(1-6C)alkyl; (iii) aryl(1-6C)alkoxy; (iv) aryloxy(1-6C)alkoxy; (v) aryloxy; (vi) aryloxy(1-6C)alkylcarbamoyl; and (vii) aryloxy(1-6C)alkylsulfamoyl; wherein the aryl moiety of groups (i) to (vii) is unsubstituted or is substituted with 1, 2 or 3 substituents.

15. A compound of the formula (I) as claimed in Claim 1, or a pharmaceutically acceptable salt thereof, wherein R_3 is hydrogen and R_4 is aryl bearing 1 substituent independently selected from (i) aryl(1-6C)alkyl; (ii) aryloxy(1-6C)alkyl; (iii) aryl(1-6C)alkoxy; (iv) aryloxy(1-6C)alkoxy; (v) aryloxy; (vi) aryloxy(1-6C)alkylcarbamoyl; and (vii) aryloxy(1-6C)alkylsulfamoyl; wherein the aryl moiety of groups (i) to (vii) is unsubstituted or is substituted with 1, 2 or 3 substituents.

16. A pharmaceutical composition which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, as claimed in Claim 1 in association with a pharmaceutically-acceptable diluent or carrier.

17. A compound of the formula (I) or a pharmaceutically acceptable salt thereof, as claimed in Claim 1 for use in a method of prophylactic or therapeutic treatment of diabetes mellitus.in a warm-blooded animal, such as man.

18. A compound of the formula (I) or a pharmaceutically acceptable salt thereof, as claimed in Claim 1 for use as a medicament for producing a PTP1B inhibitory effect in a warm-blooded mammal, such as man.

19. The use of a compound of the formula (I), or a pharmaceutically acceptable salt thereof, as claimed in Claim 1 in the manufacture of a medicament for use in the production of a PTP1B inhibitory effect in a warm-blooded animal, such as man.

20. The use of a compound of the formula (I), or a pharmaceutically acceptable salt thereof, as claimed in Claim 1 in the manufacture of a medicament for use in the treatment of diabetes mellitus.

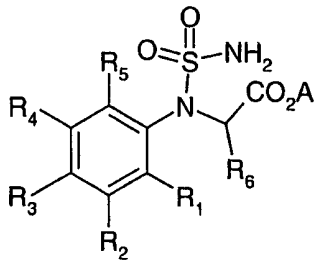
21. A method for producing a PTP1B inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as claimed in Claim 1.

22. A method for treating diabetes mellitus in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as claimed in Claim 1.

23. The use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as claimed in Claim 1 as a pharmacological tool in the development and standardisation of in vitro and in vivo test systems for the evaluation of the effects of inhibitors of PTP1B in laboratory animals.

24. A process for preparing a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of Claims 1 to 15 which process comprises of:

(a) cyclisation of a compound of the formula (II)

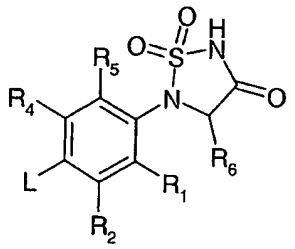


(II)

wherein A is a (1-6C)alkyl, aryl or aryl(1-6C)alkyl group, such as methyl, ethyl or benzyl, or A is a linking group to a solid phase resin, for example polystyrene/Wang resin;

(b) for compounds wherein R_3 is an optionally substituted aryl, optionally substituted biaryl, or optionally substituted heteroaryl group,

reacting a compound of formula (III):

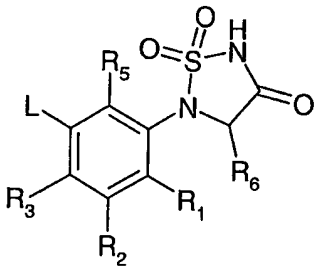


(III)

wherein L is a displaceable group, with a boronic acid of formula R_3-$B(OH)_2$, or ester thereof, or with a compound of the formula R_3-$Sn(Q_1)(Q_2)(Q_3)$ wherein Q_1, Q_2 and Q_3 are independently selected from (1-6C)alkyl and phenyl, the latter optionally substituted by a (1-4C)alkyl, (1-4C)alkoxy or halogeno group, in the presence of a suitable catalyst;

(c) for compounds wherein R_4 is an optionally substituted aryl, optionally substituted biaryl, or optionally substituted heteroaryl group,

reacting a compound of formula (IV):



(IV)

wherein L is a displaceable group, with a boronic acid of formula R_4-$B(OH)_2$, or ester thereof, or with a compound of the formula R_4-$Sn(Q_1)(Q_2)(Q_3)$ wherein Q_1, Q_2 and Q_3 have the meanings defined in (b) above, in the presence of a suitable catalyst;

and thereafter if necessary or desirable:

i) converting a compound of the formula (I) into another compound of the formula (I);

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/GB 03/04721

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D285/10 C07D417/10 A61K31/433 A61K31/4427 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 40017 A (NOVONORDISK AS) 30 October 1997 (1997-10-30) cited in the application see especially definitions of L and A1	1-24
P,X	WO 03 082841 A (NOVARTIS PHARMA GMBH ;NOVARTIS AG (CH); COPPOLA GARY MARK (US); DA) 9 October 2003 (2003-10-09) see definitions of claim 7	1-24

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 January 2004	23/01/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scruton-Evans, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 03/04721

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	BRIGHT S W ET AL: "Competitive particle concentration fluorescence immunoassays for measuring anti-diabetic drug levels in mouse plasma" JOURNAL OF IMMUNOLOGICAL METHODS, ELSEVIER SCIENCE PUBLISHERS B.V.,AMSTERDAM, NL, vol. 207, no. 1, 22 August 1997 (1997-08-22), pages 23-31, XP004093137 ISSN: 0022-1759 see compound 12, Table 4 ---	1-24
A	WO 96 16951 A (SANOFI WINTHROP INC) 6 June 1996 (1996-06-06) the whole document -----	1-24

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/GB 03/04721

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 21,22 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Ir ional Application No
PCT/GB 03/04721

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9740017	A	30-10-1997	AU	2381397 A	12-11-1997
			WO	9740017 A2	30-10-1997
			JP	2000511883 T	12-09-2000
			US	5972978 A	26-10-1999
			US	6080770 A	27-06-2000
			US	6063800 A	16-05-2000
			US	5958957 A	28-09-1999
			ZA	9703349 A	20-01-1998
WO 03082841	A	09-10-2003	WO	03082841 A1	09-10-2003
WO 9616951	A	06-06-1996	US	5556909 A	17-09-1996
			AU	703622 B2	25-03-1999
			AU	4371096 A	19-06-1996
			CA	2205837 A1	06-06-1996
			CN	1173175 A	11-02-1998
			EP	0801648 A1	22-10-1997
			FI	972306 A	30-05-1997
			HU	77364 A2	30-03-1998
			JP	10509979 T	29-09-1998
			NO	972449 A	22-07-1997
			NZ	298266 A	25-11-1998
			WO	9616951 A1	06-06-1996